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(71) Applicants *(for all designated States except US)*: **TRANSFORM PHARMACEUTICALS, INC.** [US/US]; 29 Hartwell Avenue, Lexington, MA 02421 (US). **UNIVERSITY OF SOUTH FLORIDA** [US/US]; Division of Patents and Licensing, 4202 East Flower Avenue, FAO 126, Tampa, FL 33620-7900 (US). **THE REGENTS OF THE UNIVERSITY OF MICHIGAN** [US/US]; Office of Technology Transfer, Wolverine Tower, 3003 South State St., Suite 2071, Ann Arbor, MI 48109-1280 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **ALMARSSON, Örn** [IS/US]; 22 Farmington Drive, Shrewsbury, MA 01545 (US). **BOURGHOL HICKEY, Magali** [US/US]; 342 Malden Street, Medford, MA 02155 (US). **PETERSON, Matthew** [US/US]; 60 Linda Avenue, Framingham, MA 01701 (US). **ZAWOROTKO, Michael, J.** [US/US]; 4202 E. Fowler Ave (USF30244), Tampa, FL 3362 (US). **MOULTON, Brian** [US/US]; 324 Brook St., Box II, Providence, RI 02912 (US). **RODRIGUEZ-HORNEDO, Nair** [US/US]; 1690 Northbrook Drive, Ann Arbor, MI 48103 (US).

(74) Agents: **EISENSCHENK, Frank, C.** et al.; Saliwanchik, Lloyd & Saliwanchik, 2421 N.W. 41st Street, Suite A-1, Gainsville, FL 32606-6669 (US).

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(54) **Title:** PHARMACEUTICAL CO-CRYSTAL COMPOSITIONS OF DRUGS SUCH AS CARBAMAZEPTINE, CELECOXIB, OLANZAPINE, ITRACONAZOLE, TOPIRAMATE, MODAFINIL, 5-FLUOROURACIL, HYDROCHLOROTHIAZIDE, ACETAMINOPHEN, ASPIRIN, FLURBIPROFEN, PHENYTOIN AND IBUPROFEN

(57) **Abstract:** A pharmaceutical composition comprising a co-crystal of an API and a co-crystal forming compound; wherein the API has at least one functional group selected from ether, thioether, alcohol, thiol, aldehyde, ketone, thioketone, nitrate ester, phosphate ester, thiophosphate ester, ester, thioester, sulfate ester, carboxylic acid, phosphonic acid, phosphinic acid, sulfonic acid, amide, primary amine, secondary amine, ammonia, tertiary amine, sp2 amine, thiocyanate, cyanamide, oxime, nitrile diazo, organohalide, nitro, s-heterocyclic ring, thiophene, n-heterocyclic ring, pyrrole, oheterocyclic ring, furan, epoxide, peroxide, hydroxamic acid, imidazole, pyridine and the co-crystal forming compound has at least one functional group selected from amine, amide, pyridine, imidazole, indole, pyrrolidine, carbonyl, carboxyl, hydroxyl, phenol, sulfone, sulfonyl, mercapto and methyl thio, such that the API and co-crystal forming compound are capable of co-crystallizing from a solution phase under crystallization conditions.

PHARMACEUTICAL CO-CRYSTAL COMPOSITIONS OF DRUGS SUCH AS CARBAMAZEPTINE, CELECOXIB, OLANZAPINE, ITRACONAZOLE, TOPIRAMATE, MODAFINIL, 5-FLUOROURACIL, HYDROCHLOROTHIAZIDE, ACETAMINOPHEN, ASPIRIN, FLURBIPROFEN, PHENYTOIN AND IBUPROFEN

INCORPORATION BY REFERENCE

The content of US Patent Application No. 60/451,213 filed on February 28, 2003 is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

The present invention relates to co-crystal API-containing compositions, pharmaceutical compositions comprising such APIs, and methods for preparing the same.

BACKGROUND OF THE INVENTION

Active pharmaceutical ingredients (API or APIs (plural)) in pharmaceutical compositions can be prepared in a variety of different forms. Such APIs can be prepared so as to have a variety of different chemical forms including chemical derivatives or salts. Such APIs can also be prepared to have different physical forms. For example, the APIs may be amorphous, may have different crystalline polymorphs, or may exist in different solvation or hydration states. By varying the form of an API, it is possible to vary the physical properties thereof. For example, crystalline polymorphs typically have different solubilities from one another, such that a more thermodynamically stable polymorph is less soluble than a less thermodynamically stable polymorph. Pharmaceutical polymorphs can also differ in properties such as shelf-life, bioavailability, morphology, vapour pressure, density, colour, and compressibility. Accordingly, variation of the crystalline state of an API is one of many ways in which to modulate the physical properties thereof.

It would be advantageous to have new forms of these APIs that have improved properties, in particular, as oral formulations. Specifically, it is desirable to identify improved forms of APIs that exhibit significantly improved properties including increased aqueous solubility and stability. Further, it is desirable to improve the processability, or preparation of pharmaceutical formulations. For example, needle-like crystal forms or habits of APIs can cause aggregation, even in compositions where the API is mixed with other substances, such that a non-uniform mixture is obtained. It is also desirable to increase the dissolution rate of API-containing pharmaceutical compositions in water, increase the bioavailability of orally-

administered compositions, and provide a more rapid onset to therapeutic effect. It is also desirable to have a form of the API which, when administered to a subject, reaches a peak plasma level faster, has a longer lasting therapeutic plasma concentration, and higher overall exposure when compared to equivalent amounts of the API in its presently-known form.

SUMMARY OF THE INVENTION

It has now been found that new co-crystalline forms of APIs can be obtained which improve the properties of APIs as compared to such APIs in a non-co-crystalline state (free acid, free base, zwitter ions, salts, etc.).

Accordingly, in a first aspect, the present invention provides a co-crystal pharmaceutical composition comprising an API compound and a co-crystal forming compound, such that the API and co-crystal forming compound are capable of co-crystallizing from a solid or solution phase under crystallization conditions.

Another aspect of the present invention provides a process for the production of a pharmaceutical composition, which process comprises:

(1) providing an API which has at least one functional group selected from ether, thioether, alcohol, thiol, aldehyde, ketone, thioketone, nitrate ester, phosphate ester, thiophosphate ester, ester, thioester, sulfate ester, carboxylic acid, phosphonic acid, phosphinic acid, sulfonic acid, amide, primary amine, secondary amine, ammonia, tertiary amine, sp2 amine, thiocyanate, cyanamide, oxime, nitrile, diazo, organohalide, nitro, s-heterocyclic ring, thiophene, n-heterocyclic ring, pyrrole, o-heterocyclic ring, furan, epoxide, peroxide, hydroxamic acid, imidazole, and pyridine;

(2) providing a co-crystal forming compound which has at least one functional group selected from ether, thioether, alcohol, thiol, aldehyde, ketone, thioketone, nitrate ester, phosphate ester, thiophosphate ester, ester, thioester, sulfate ester, carboxylic acid, phosphonic acid, phosphinic acid, sulfonic acid, amide, primary amine, secondary amine, ammonia, tertiary amine, sp2 amine, thiocyanate, cyanamide, oxime, nitrile, diazo, organohalide, nitro, s-heterocyclic ring, thiophene, n-heterocyclic ring, pyrrole, o-heterocyclic ring, furan, epoxide, peroxide, hydroxamic acid, imidazole, and pyridine;

(3) grinding, heating or contacting in solution the API with the co-crystal forming compound under crystallization conditions;

(4) isolating co-crystals formed thereby; and

(5) incorporating the co-crystals into a pharmaceutical composition.

A further aspect of the present invention provides a process for the production of a pharmaceutical composition, which comprises:

(1) grinding, heating or contacting in solution an API compound with a co-crystal forming compound, under crystallization conditions, so as to form a solid phase;

(2) isolating co-crystals comprising the API and the co-crystal forming compound; and

(3) incorporating the co-crystals into a pharmaceutical composition.

In a further aspect, the present invention provides a process for the production of a pharmaceutical composition, which comprises:

(1) providing (*i*) an API or a plurality of different APIs, and (*ii*) a co-crystal forming compound or a plurality of different co-crystal forming compounds, wherein at least one of the APIs and the co-crystal forming compounds is provided as a plurality thereof;

(2) isolating co-crystals comprising the API and the co-crystal forming compound; and

(3) incorporating the co-crystals into a pharmaceutical composition.

Solubility Modulation

In a further aspect, the present invention provides a process for modulating the solubility of an API, which process comprises:

(1) grinding, heating or contacting in solution the API with a co-crystal forming compound under crystallization conditions, so as to form a co-crystal of the API and the co-crystal forming compound; and

(2) isolating co-crystals comprising the API and the co-crystal forming compound.

Dissolution Modulation

In a further aspect, the present invention provides a process for modulating the dissolution of an API, whereby the aqueous dissolution rate or the dissolution rate in

simulated gastric fluid or in simulated intestinal fluid, or in a solvent or plurality of solvents is increased or decreased, which process comprises:

(1) grinding, heating or contacting in solution the API with a co-crystal forming compound under crystallization conditions, so as to form a co-crystal of the API and the co-crystal forming compound; and

(2) isolating co-crystals comprising the API and the co-crystal forming compound.

In one embodiment, the dissolution of the API is increased.

Bioavailability Modulation

In a further aspect, the present invention provides a process for modulating the bioavailability of an API, whereby the AUC is increased, the time to T_{max} is reduced, the length of time the concentration of the API is above ½ T_{max} is increased, or C_{max} is increased, which process comprises:

(1) grinding, heating or contacting in solution the API with a co-crystal forming compound under crystallization conditions, so as to form a co-crystal of the API and the co-crystal forming compound; and

(2) isolating co-crystals comprising the API and the co-crystal forming compound.

Dose Response Modulation

In a further aspect the present invention provides a process for improving the linearity of a dose response of an API, which process comprises:

(1) grinding, heating, or contacting in solution an API with a co-crystal forming compound under crystallization conditions, so as to form a co-crystal of the API and the co-crystal forming compound; and

(2) isolating co-crystals comprising the API and the co-crystal forming compound.

Increased Stability

In a still further aspect the present invention provides a process for improving the stability of a pharmaceutical salt, which process comprises:

(1) grinding, heating or contacting in solution the pharmaceutical salt with a co-crystal forming compound under crystallization conditions, so as to form a co-crystal of the API and the co-crystal forming compound; and

(2) isolating co-crystals comprising the API and the co-crystal forming compound.

Difficult to Salt or Unsaltable Compounds

In a still further aspect the present invention provides a process for making co-crystals of difficult to salt or unsaltable APIs, which process comprises:

(1) grinding, heating or contacting in solution the API with a co-crystal forming compound under crystallization conditions, so as to form a co-crystal of the API and the co-crystal forming compound; and

(2) isolating co-crystals comprising the API and the co-crystal forming compound.

Decreasing Hygroscopicity

In a still further aspect the present invention provides a method for decreasing the hygroscopicity of an API, which method comprises:

(1) grinding, heating or contacting in solution the API with a co-crystal forming compound under crystallization conditions, so as to form a co-crystal of the API and the co-crystal forming compound; and

(2) isolating co-crystals comprising the API and the co-crystal forming compound.

Crystallizing Amorphous Compounds

In a still further embodiment aspect the present invention provides a process for crystallizing an amorphous compound, which process comprises:

(1) grinding, heating or contacting in solution the API with a co-crystal forming compound under crystallization conditions, so as to form a co-crystal of the API and the co-crystal forming compound; and

(2) isolating co-crystals comprising the API and the co-crystal forming compound.

Decreasing Form Diversity

In a still further embodiment aspect the present invention provides a process for reducing the form diversity of an API, which process comprises:

(1) grinding, heating or contacting in solution the API with a co-crystal forming compound under crystallization conditions, so as to form a co-crystal of the API and the co-crystal forming compound; and

(2) isolating co-crystals comprising the API and the co-crystal forming compound.

Morphology Modulation

In a still further embodiment aspect the present invention provides a process for modifying the morphology of an API, which process comprises:

(1) grinding, heating or contacting in solution the API with a co-crystal forming compound under crystallization conditions, so as to form a co-crystal of the API and the co-crystal forming compound; and

(2) isolating co-crystals comprising the API and the co-crystal forming compound.

In a further aspect, the present invention provides a co-crystal composition comprising a co-crystal, wherein said co-crystal comprises an API compound and a co-crystal forming compound. In further embodiments the co-crystal has an improved property as compared to the free form (including a free acid, free base, zwitter ion, hydrate, solvate, etc.) or a salt (which includes salt hydrates and solvates). In further embodiments, the improved property is selected from the group consisting of: increased solubility, increased dissolution, increased bioavailability, increased dose response, decreased hygroscopicity, a crystalline form of a normally amorphous compound, a crystalline form of a difficult to salt or unsaltable compound, decreased form diversity, more desired morphology, or other property described herein.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 PXRD pattern for a co-crystal of carbamazepine and saccharin (Form I)

Fig. 2 DSC thermogram for a co-crystal of carbamazepine and saccharin (Form I)

Fig. 3 PXRD pattern for a co-crystal of carbamazepine and nicotinamide (Form I)

Fig. 4 DSC thermogram for a co-crystal of carbamazepine and nicotinamide (Form I)

Fig. 5 PXRD pattern for a co-crystal of carbamazepine and trimesic acid (Form I)

Fig. 6 PXRD pattern for a co-crystal of topiramate and 18-crown-6

Fig. 7 DSC thermogram for a co-crystal of topiramate and 18-crown-6

Fig. 8 PXRD pattern for a co-crystal of olanzapine and nicotinamide (Form I)

Fig. 9 DSC thermogram for a co-crystal of olanzapine and nicotinamide (Form I)

Fig. 10 PXRD pattern for a co-crystal of celecoxib and 18-crown-6

Fig. 11 DSC thermogram for a co-crystal of celecoxib and 18-crown-6

Fig. 12 PXRD pattern for a co-crystal of itraconazole and succinic acid

Fig. 13 DSC thermogram for a co-crystal of itraconazole and succinic acid

Fig. 14 PXRD pattern for a co-crystal of itraconazole and fumaric acid

Fig. 15 DSC thermogram for a co-crystal of itraconazole and fumaric acid

Fig. 16 PXRD pattern for a co-crystal of itraconazole and tartaric acid

Fig. 17 DSC thermogram for a co-crystal of itraconazole and tartaric acid

Fig. 18 PXRD pattern for a co-crystal of itraconazole and malic acid

Fig. 19 DSC thermogram for a co-crystal of itraconazole and malic acid

Fig. 20 PXRD pattern for a co-crystal of itraconazoleHCl and tartaric acid

Fig. 21 DSC thermogram for a co-crystal of itraconazoleHCl and tartaric acid

Fig. 22 PXRD pattern for a co-crystal of modafinil and malonic acid

Fig. 23 PXRD pattern for a co-crystal of modafinil and benzamide

Fig. 24 PXRD pattern for a co-crystal of modafinil and mandelic acid

Fig. 25 PXRD pattern for a co-crystal of modafinil and glycolic acid

Fig. 26 PXRD pattern for a co-crystal of modafinil and fumaric acid

Fig. 27 Dissolution profile for a co-crystal of celecoxib:nicotinamide vs. celecoxib free acid

Fig. 28 Dissolution profile for co-crystals of itraconazole:succinic acid, itraconazle:tartaric acid and itraconazole:malic acid vs. itraconazole free base

Fig. 29 Hygroscopicity profile for a co-crystal of celecoxib:nicotinamide vs. celecoxib sodium

Fig. 30 PXRD pattern for a co-crystal of olanzapine and nicotinamide (Form II)

Fig. 31 PXRD pattern for a co-crystal of olanzapine and nicotinamide (Form III)

Fig. 32A-D Packing diagrams and crystal structure of olanzapine and nicotinamide (Form III)

Fig. 33 DSC thermogram for a co-crystal of 5-fluorouracil and urea

Fig. 34 TGA thermogram for a co-crystal of 5-fluorouracil and urea

Fig. 35 Raman spectrum for a co-crystal of 5-fluorouracil and urea

Fig. 36 PXRD pattern for a co-crystal of 5-fluorouracil and urea

Fig. 37 PXRD pattern for a co-crystal of hydrochlorothiazide and nicotinic acid

Fig. 38 PXRD pattern for a co-crystal of hydrochlorothiazide and 18-crown-6

Fig. 39 PXRD pattern for a co-crystal of hydrochlorothiazide and piperazine

Fig. 40 DSC thermogram for a co-crystal of modafinil and malonic acid

Fig. 41 TGA thermogram for a co-crystal of modafinil and malonic acid

Fig. 42 Raman spectrum for a co-crystal of modafinil and malonic acid

Fig. 43 PXRD pattern for a co-crystal of modafinil and maleic acid

Fig. 44A–B An acetaminophen 1-D polymeric chain and a co-crystal of acetaminophen and 4,4'-bipyridine, respectively.

Fig. 45A-B Pure phenytoin and a co-crystal with phenytoin and pyridone, respectively.

Fig. 46A-D Pure aspirin and the corresponding crystal structure are shown in Figures 46A and 46B, respectively. Figures 46C and 46D show the supramolecular entity containing the synthon and corresponding co-crystal of aspirin and 4,4'-bipyridine, respectively.

Fig. 47A-D Pure ibuprofen and the corresponding crystal structure are shown in Figures 7A and 7B, respectively. Figures 7C and 7D show the supramolecular entity containing the synthon and corresponding co-crystal of ibuprofen and 4,4'-bipyridine, respectively.

Fig. 48A-D Pure flurbiprofen and the corresponding crystal structure are shown in Figures 48A and 48B, respectively. Figures 5C and 5D show the supramolecular synthon and corresponding co-crystal of flurbiprofen and 4,4'-bipyridine, respectively.

Fig. 49A-B The supramolecular entity containing the synthon and the corresponding co-crystal structure of flurbiprofen and trans-1,2-bis(4-pyridyl)ethylene, respectively.

Fig. 50A-B The crystal structure of pure carbamazepine and the co-crystal structure of carbamazepine and *p*-phthalaldehyde, respectively.

Fig. 51 The co-crystal structure of carbamazepine and nicotinamide (Form II).

Fig. 52 The co-crystal structure of carbamazepine and saccharin (Form II).

Fig. 53A-C The chemical structures of ibuprofen, flurbiprofen, and aspirin, respectively.

Fig. 54A-B The crystal structure of carbamazepine and the co-crystal structure of carbamazepine and 2,6-pyridinedicarboxylic acid, respectively.

Fig. 55A-B The crystal structure of carbamazepine and the co-crystal structure of carbamazepine and 5-nitroisophthalic acid, respectively.

Fig. 56A-B The crystal structure of carbamazepine and the co-crystal structure of carbamazepine and 1,3,5,7-adamantanetetracarboxylic acid, respectively.

Fig. 57A-B The crystal structure of carbamazepine and the co-crystal structure of carbamazepine and benzoquinone, respectively.

Fig. 58A-B The crystal structure of carbamazepine and the co-crystal structure of carbamazepine and trimesic acid (Form II), respectively.

Fig. 59 PXRD diffractogram for a co-crystal of celecoxib and nicotinamide

Fig. 60 DSC thermogram for a co-crystal of celecoxib and nicotinamide

Fig. 61 TGA thermogram for a co-crystal of celecoxib and nicotinamide

Fig. 62 Raman spectrum for a co-crystal of celecoxib and nicotinamide

Fig. 63 Hydrogen-bonding motifs observed in co-crystals

DETAILED DESCRIPTION OF THE INVENTION

The term "co-crystal" as used herein means a crystalline material comprised of two or more unique solids at room temperature, each containing distinctive physical characteristics, such as structure, melting point and heats of fusion, with the exception that, if specifically stated, the API may be a liquid at room temperature. The co-crystals of the present invention comprise a co-crystal former H-bonded to an API. The co-crystal former may be H-bonded directly to the API or may be H-bonded to an additional molecule which is bound to the API. The additional molecule may be H-bonded to the API or bound ionically or covalently to the API. The additional

molecule could also be a different API. Solvates of API compounds that do not further comprise a co-crystal forming compound are not co-crystals according to the present invention. The co-crystals may however, include one or more solvate molecules in the crystalline lattice. That is, solvates of co-crystals, or a co-crystal further comprising a solvent or compound that is a liquid at room temperature, is included in the present invention, but crystalline material comprised of only one solid and one or more liquids (at room temperature) are not included in the present invention, with the previously noted exception of specifically stated liquid APIs. The co-crystals may also be a co-crystal between a co-crystal former and a salt of an API, but the API and the co-crystal former of the present invention are constructed or bonded together through hydrogen bonds. Other modes of molecular recognition may also be present including, pi-stacking, guest-host complexation and van der Waals interactions. Of the interactions listed above, hydrogen-bonding is the dominant interaction in the formation of the co-crystal, (and a required interaction according to the present invention) whereby a non-covalent bond is formed between a hydrogen bond donor of one of the moieties and a hydrogen bond acceptor of the other. Hydrogen bonding can result in several different intermolecular configurations. For example, hydrogen bonds can result in the formation of dimers, linear chains, or cyclic structures. These configurations can further include extended (two-dimensional) hydrogen bond networks and isolated triads (Fig. 63). An alternative embodiment provides for a co-crystal wherein the co-crystal former is a second API. In another embodiment, the co-crystal former is not an API. In another embodiment the co-crystal comprises two co-crystal formers. Co-crystals may also be formed where the API is a "guest" molecule in regions of a crystalline lattice formed by the co-crystal forming compound, thus forming an inclusion complex. For purposes of the present invention, the chemical and physical properties of an API in the form of a co-crystal may be compared to a reference compound that is the same API in a different form. The reference compound may be specified as a free form, or more specifically, a free acid, free base, or zwitter ion; a salt, or more specifically for example, an inorganic base addition salt such as sodium, potassium, lithium, calcium, magnesium, ammonium, aluminum salts or organic base addition salts, or an inorganic acid addition salts such as HBr, HCl, sulfuric, nitric, or phosphoric acid addition salts or an organic acid addition salt such as acetic, proprionic, pyruvic, malanic, succinic, malic, maleic, fumaric, tartaric, citric, benzoic, methanesulfonic,

ethanesulforic, stearic or lactic acid addition salt; an anhydrate or hydrate of a free form or salt, or more specifically, for example, a hemihydrate, monohydrate, dihydrate, trihydrate, quadrahydrate, pentahydrate; or a solvate of a free form or salt. The reference compound may also be specified as crystalline or amorphous.

According to the present invention, the co-crystals can include an acid addition salt or base addition salt of an API. Acid addition salts include, but are not limited to, inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, and phosphoric acid, and organic acids such as acetic acid, propionic acid, hexanoic acid, heptanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartatic acid, citric acid, benzoic acid, o-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, madelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, p-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, p-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo[2.2.2]oct-2-ene-1-carboxylic acid, glucoheptonic acid, 4,4'-methylenebis(3-hydroxy-2-ene-1-carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutaric acid, hydroxynaphthoic acid, salicylic acid, stearic acid, and muconic acid. Base addition salts include, but are not limited to, inorganic bases such as sodium, potassium, lithium, ammonium, calcium and magnesium salts, and organic bases such as primary, secondary and tertiary amines (e.g. isopropylamine, trimethyl amine, diethyl amine, tri(iso-propyl) amine, tri(n-propyl) amine, ethanolamine, 2-dimethylaminoethanol, tromethamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, N-alkylglucamines, theobromine, purines, piperazine, piperidine, morpholine, and N-ethylpiperidine).

The ratio of API to co-crystal former may be stoichiometric or non-stoichiometric according to the present invention. For example, 1:1, 1:1.5 and 1:2 ratios of API:co-crystal former are acceptable.

It has surprisingly been found that when an API and a selected co-crystal forming compound are allowed to form co-crystals, the resulting co-crystals give rise to improved properties of the API, as compared to the API in a free form (including free acids, free bases, and zwitter ions, hydrates, solvates, etc.), or an acid or base salt thereof particularly with respect to: solubility, dissolution, bioavailability, stability, Cmax, Tmax, processability, longer lasting therapeutic plasma concentration,

hygroscopicity, crystallization of amorphous compounds, decrease in form diversity (including polymorphism and crystal habit), change in morphology or crystal habit, etc. For example, a co-crystal form of an API is particularly advantageous where the original API is insoluble or sparingly soluble in water. Additionally, the co-crystal properties conferred upon the API are also useful because the bioavailability of the API can be improved and the plasma concentration and/or serum concentration of the API can be improved. This is particularly advantageous for orally-administrable formulations. Moreover, the dose response of the API can be improved, for example by increasing the maximum attainable response and/or increasing the potency of the API by increasing the biological activity per dosing equivalent.

Accordingly, in a first aspect, the present invention provides a pharmaceutical composition comprising a co-crystal of an API and a co-crystal forming compound, such that the API and co-crystal forming compound are capable of co-crystallizing from a solution phase under crystallization conditions or from the solid-state, for example, through grinding or heating. In another aspect, the API has at least one functional group selected from ether, thioether, alcohol, thiol, aldehyde, ketone, thioketone, nitrate ester, phosphate ester, thiophosphate ester, ester, thioester, sulfate ester, carboxylic acid, phosphonic acid, phosphinic acid, sulfonic acid, amide, primary amine, secondary amine, ammonia, tertiary amine, sp2 amine, thiocyanate, cyanamide, oxime, nitrile, diazo, organohalide, nitro, s-heterocyclic ring, thiophene, n-heterocyclic ring, pyrrole, o-heterocyclic ring, furan, epoxide, peroxide, hydroxamic acid, imidazole, and pyridine anda co-crystal forming compound which has at least one functional group selected from ether, thioether, alcohol, thiol, aldehyde, ketone, thioketone, nitrate ester, phosphate ester, thiophosphate ester, ester, thioester, sulfate ester, carboxylic acid, phosphonic acid, phosphinic acid, sulfonic acid, amide, primary amine, secondary amine, ammonia, tertiary amine, sp2 amine, thiocyanate, cyanamide, oxime, nitrile, diazo, organohalide, nitro, s-heterocyclic ring, thiophene, n-heterocyclic ring, pyrrole, o-heterocyclic ring, furan, epoxide, peroxide, hydroxamic acid, imidazole, and pyridine, or a functional group in a Table herein, such that the API and co-crystal forming compound are capable of co-crystallizing from a solution phase under crystallization conditions.

The co-crystals of the present invention are formed where the API and co-crystal forming compound are bonded together through hydrogen bonds. Other non-

covalent interactions, including pi-stacking and van der Waals interactions, may also be present.

In one embodiment, the co-crystal former is selected from the co-crystal formers of Table I and Table II. In other embodiments, the co-crystal former of Table I is specified as a Class 1, Class 2, or Class 3 co-crystal former (see column labeled "class" Table I). In another embodiment, the difference in pK_a value of the co-crystal former and the API is less than 2. In other embodiments, the difference in pK_a values of the co-crystal former and API is less than 3, less than 4, less than 5, between 2 and 3, between 3 and –4, or between 4 and 5. Table I lists multiple pK_a values for co-crystal formers having multiple functionalities. It is readily apparent to one skilled in the art the particular functional group corresponding to a particular pK_a value.

In another embodiment the particular functional group of a co-crystal former interacting with the API is specified (see for example Table I, columns labeled "Functionality" and "Molecular Structure" and the column of Table II labeled "Co-Crystal Former Functional Group"). In a further embodiment the functional group of the API interacting with the co-crystal former functional group is specified (see, for example, Tables II and III).

In another embodiment, the co-crystal comprises more than one co-crystal former. For example, two, three, four, five, or more co-crystal formers can be incorporated in a co-crystal with an API. Co-crystals which comprise two or more co-crystal formers and an API are bound together via hydrogen bonds. In one embodiment, incorporated co-crystal formers are hydrogen bonded to the API molecules. In another embodiment, co-crystal formers are hydrogen bonded to either the API molecules or the incorporated co-crystal formers.

In a further embodiment, several co-crystal formers can be contained in a single compartment, or kit, for ease in screening an API for potential co-crystal species. The co-crystal kit can comprise 5, 10, 15, 20, 25, 30, 40, 50, 60, 70, 80, 90, 100, or more of the co-crystal formers in Tables I and II. The co-crystal formers are in solid form and in an array of individual reaction vials such that individual co-crystal formers can be tested with one or more APIs by one or more crystallization methods or multiple co-crystal formers can be easily tested against one or more compounds by one or more crystallization methods. The crystallization methods include, but are not limited to, melt recrystallization, grinding, milling, standing, co-crystal formation from solution by evaporation, thermally driven crystallization from solution, co-crystal

formation from solution by addition of anti-solvent, co-crystal formation from solution by vapor-diffusion, co-crystal formation from solution by drown-out, co-crystal formation from solution by any combination of the above mentioned techniques, co-crystal formation by co-sublimation, co-crystal formation by sublimation using a Knudsen cell apparatus, co-crystal formation by standing the desired components of the co-crystal in the presence of solvent vapor, co-crystal formation by slurry conversion of the desired components of the co-crystal in a solvent or mixtures of solvents, or co-crystal formation by any combination of the above techniques in the presence of additives, nucleates, crystallization enhancers, precipitants, chemical stabilizers, or anti-oxidants. The co-crystallization kits can be used alone or as part of larger crystallization experiments. For example, kits can be constructed as single co-crystal former single well kits, single co-crystal former multi-well kits, multi-co-crystal former single well kits, or multi-co-crystal former multi-well kits.

In a further embodiment, the API is selected from an API of Table IV or elsewhere herein. For pharmaceuticals listed in Table IV, co-crystals can comprise such APIs in free form (i.e. free acid, free base, zwitter ion), salts, solvates, hydrates, or the like. For APIs in Table IV listed as salts, solvates, hydrates, and the like, the API can either be of the form listed in Table IV or its corresponding free form, or of another form that is not listed. Table IV includes the CAS number, chemical name, or a PCT or patent reference (each incorporated herein in their entireties). In further embodiments, the functional group of the particular API interacting with the co-crystal former is specified. A specific functional group of a co-crystal former, a specific co-crystal former, or a specified functional group or a specific co-crystal former interacting with the particular API may also be specified. It is noted that for Table II, the co-crystal former, and optionally the specific functionality, and each of the listed corresponding interacting groups are included as individual species of the present invention. Thus, each specific combination of a co-crystal former and one of the interacting groups in the same row may be specified as a species of the present invention. The same is true for other combinations as discussed in the Tables and elsewhere herein.

In each process according to the invention, there is a need to contact the API with the co-crystal forming compound. This may involve grinding the two solids together or melting one or both components and allowing them to recrystallize. This

may also involve either solubilizing the API and adding the co-crystal forming compound, or solubilizing the co-crystal forming compound and adding the API. Crystallization conditions are applied to the API and co-crystal forming compound. This may entail altering a property of the solution, such as pH or temperature and may require concentration of the solute, usually by removal of the solvent, typically by drying the solution. Solvent removal results in the concentration of both API and co-crystal former increasing over time so as to facilitate crystallization. Once the solid phase comprising any crystals is formed, this may be tested as described herein.

The co-crystals obtained as a result of such process steps may be readily incorporated into a pharmaceutical composition by conventional means. Pharmaceutical compositions in general are discussed in further detail below and may further comprise a pharmaceutically-acceptable diluent, excipient or carrier.

In a further aspect, the present invention provides a process for the production of a pharmaceutical composition, which process comprises:

(1) providing an API which has at least one functional group selected from ether, thioether, alcohol, thiol, aldehyde, ketone, thioketone, nitrate ester, phosphate ester, thiophosphate ester, ester, thioester, sulfate ester, carboxylic acid, phosphonic acid, phosphinic acid, sulfonic acid, amide, primary amine, secondary amine, ammonia, tertiary amine, sp2 amine, thiocyanate, cyanamide, oxime, nitrile diazo, organohalide, nitro, s-heterocyclic ring, thiophene, n-heterocyclic ring, pyrrole, o-heterocyclic ring, furan, epoxide, peroxide, hydroxamic acid, imidazole, and pyridine or of Table II or III;

(2) providing a co-crystal former which has at least one functional group selected from ether, thioether, alcohol, thiol, aldehyde, ketone, thioketone, nitrate ester, phosphate ester, thiophosphate ester, ester, thioester, sulfate ester, carboxylic acid, phosphonic acid, phosphinic acid, sulfonic acid, amide, primary amine, secondary amine, ammonia, tertiary amine, sp2 amine, thiocyanate, cyanamide, oxime, nitrile, diazo, organohalide, nitro, s-heterocyclic ring, thiophene, n-heterocyclic ring, pyrrole, o-heterocyclic ring, furan, epoxide, peroxide, hydroxamic acid, imidazole, and pyridine or of Table I, II, or III;

(3) grinding, heating or contacting in solution the API with the co-crystal forming compound under crystallization conditions;

(4) isolating co-crystals formed thereby; and

(5) incorporating the co-crystals into a pharmaceutical composition.

In a still further aspect the present invention provides a process for the production of a pharmaceutical composition, which comprises:

(1) grinding, heating or contacting in solution an API with a co-crystal forming compound, under crystallization conditions, so as to form a solid phase;

(2) isolating co-crystals comprising the API and the co-crystal forming compound; and

(3) incorporating the co-crystals into a pharmaceutical composition.

Assaying the solid phase for the presence of co-crystals of the API and the co-crystal forming compound may be carried out by conventional methods known in the art. For example, it is convenient and routine to use powder X-ray diffraction techniques to assess the presence of co-crystals. This may be affected by comparing the spectra of the API, the crystal forming compound and putative co-crystals in order to establish whether or not true co-crystals had been formed. Other techniques, used in an analogous fashion, include differential scanning calorimetry (DSC), thermogravimetric analysis (TGA) and Raman spectroscopy. Single crystal X-ray diffraction is especially useful in identifying co-crystal structures.

In a further aspect, the present invention therefore provides a process of screening for co-crystal compounds, which comprises:

(1) providing (*i*) an API compound, and (*ii*) a co-crystal forming compound; and

(2) screening for co-crystals of APIs with co-crystal forming compounds by subjecting each combination of API and co-crystal forming compound to a step comprising:

(a) grinding, heating or contacting in solution the API with the co-crystal forming compound under crystallization conditions so as to form a solid phase; and

(b) isolating co-crystals comprising the API and the co-crystal forming compound.

An alternative embodiment is drawn to a process of screening for co-crystal compounds, which comprises:

(1) providing (*i*) an API or a plurality of different APIs, and (*ii*) a co-crystal forming compound or a plurality of different co-crystal forming compounds, wherein at least one of the API and the co-crystal forming compound is provided as a plurality thereof; and

(2) screening for co-crystals of APIs with co-crystal forming compounds by subjecting each combination of API and co-crystal forming compound to a step comprising

(a) grinding, heating or contacting in solution the API with the co-crystal forming compound under crystallization conditions so as to form a solid phase; and

(b) isolating co-crystals comprising the API and the co-crystal forming compound.

Solubility Modulation

In a further aspect, the present invention provides a process for modulating the solubility of an API, which process comprises:

(1) grinding, heating or contacting in solution the API with a co-crystal forming compound under crystallization conditions, so as to form a co-crystal of the API and the co-crystal forming compound; and

(2) isolating co-crystals comprising the API and the co-crystal forming compound.

In one embodiment, the solubility of the API is modulated such that the aqueous solubility is increased. Solubility of APIs may be measured by any conventional means such as chromatography (e.g., HPLC) or spectroscopic determination of the amount of API in a saturated solution of the API, such as UV-spectroscopy, IR-spectroscopy, Raman spectroscopy, quantitative mass spectroscopy, or gas chromatography.

In another aspect of the invention, the API may have low aqueous solubility. Typically, low aqueous solubility in the present application refers to a compound having a solubility in water which is less than or equal to 10 mg/mL, when measured at 37 degrees C, and preferably less than or equal to 5 mg/mL or 1 mg/mL. Low aqueous solubility can further be specifically defined as less than or equal to 900, 800, 700, 600, 500, 400, 300, 200 150 100, 90, 80, 70, 60, 50, 40, 30, 20 micrograms/mL, or further 10, 5 or 1 micrograms/mL, or further 900, 800, 700, 600, 500, 400, 300,

200 150, 100 90, 80, 70, 60, 50, 40, 30, 20, or 10 ng/mL, or less than 10 ng/mL when measured at 37 degrees C. Aqueous solubility can also be specified as less than 500, 400, 300, 200, 150, 100, 75, 50 or 25 mg/mL. As embodiments of the present invention, solubility can be increased 2, 3, 4, 5, 7, 10, 15, 20, 25, 50, 75, 100, 200, 300, 500, 750, 1000, 5000, or 10,000 times by making a co-crystal of the reference form (e.g., crystalline or amorphous free acid, free base or zwitter ion, hydrate or solvate), or a salt thereof. Further aqueous solubility can be measured in simulated gastric fluid (SGF) or simulated intestinal fluid (SIF) rather than water. SGF (non-diluted) of the present invention is made by combining 1 g/L Triton X-100 and 2 g/L NaCl in water and adjusting the pH with 20 mM HCl to obtain a solution with a final pH=1.7 (SIF is 0.68% monobasic potassium phosphate, 1% pancreatin, and sodium hydroxide where the pH of the final solution is 7.5). The pH of the solvent used may also be specified as 1, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, 11.5, or 12, or any pH in between successive values.

Examples of embodiments includes: co-crystal compositions with an aqueous solubility, at 37 degrees C and a pH of 7.0, that is increased at least 5 fold over the reference form, co-crystal compositions with a solubility in SGF that is increased at least 5 fold over the reference form, co-crystal compositions with a solubility in SIF that is increased at least 5 fold over the reference form.

Dissolution Modulation

In another aspect of the present invention, the dissolution profile of the API is modulated whereby the aqueous dissolution rate or the dissolution rate in simulated gastric fluid or in simulated intestinal fluid, or in a solvent or plurality of solvents is increased. Dissolution rate is the rate at which API solids dissolve in a dissolution medium. For APIs whose absorption rates are faster than the dissolution rates (e.g., steroids), the rate-limiting step in the absorption process is often the dissolution rate. Because of a limited residence time at the absorption site, APIs that are not dissolved before they are removed from intestinal absorption site are considered useless. Therefore, the rate of dissolution has a major impact on the performance of APIs that are poorly soluble. Because of this factor, the dissolution rate of APIs in solid dosage forms is an important, routine, quality control parameter used in the API manufacturing process.

Dissolution rate = K S (C_s-C)

where K is dissolution rate constant, S is the surface area, C_s is the apparent solubility, and C is the concentration of API in the dissolution medium.

For rapid API absorption, C_s-C is approximately equal to C_s

The dissolution rate of APIs may be measured by conventional means known in the art.

The increase in the dissolution rate of a co-crystal, as compared to the reference form (e.g., free form or salt), may be specified, such as by 10, 20, 30, 40, 50, 60, 70, 80, 90, or 100%, or by 2, 3, 4, 5 ,6, 7, 8, 9, 10, 15, 20, 25, 30, 40, 50, 75, 100, 125, 150, 175, 200, 250, 300, 350, 400, 500, 1000, 10,000, or 100,000 fold greater than the reference form (e.g., free form or salt form) in the same solution. Conditions under which the dissolution rate is measured is the same as discussed above The increase in dissolution may be further specified by the time the composition remains supersaturated before reaching equilibrium solubility.

Examples of above embodiments include: co-crystal compositions with a dissolution rate in aqueous solution, at 37 degrees C and a pH of 7.0, that is increased at least 5 fold over the reference form, co-crystal compositions with a dissolution rate in SGF that is increased at least 5 fold over the reference form, co-crystal compositions with a dissolution rate in SIF that is increased at least 5 fold over the reference form.

Bioavailability Modulation

The methods of the present invention are used to make a pharmaceutical API formulation with greater solubility, dissolution, and bioavailability. Bioavailability can be improved via an increase in AUC, reduced time to T_{max}, (the time to reach peak blood serum levels), or increased C_{max}. The present invention can result in higher plasma concentrations of API when compared to the neutral form or salt alone (reference form).

AUC is the area under the plot of plasma concentration of API (not logarithm of the concentration) against time after API administration. The area is conveniently determined by the "trapezoidal rule": The data points are connected by straight line segments, perpendiculars are erected from the abscissa to each data point, and the sum

of the areas of the triangles and trapezoids so constructed is computed. When the last measured concentration (C_n, at time t_n) is not zero, the AUC from t_n to infinite time is estimated by C_n/k_{el}.

The AUC is of particular use in estimating bioavailability of APIs, and in estimating total clearance of APIs (Cl_T). Following single intravenous doses, AUC = D/Cl_T, for single compartment systems obeying first-order elimination kinetics, where D is the dose; alternatively, AUC = C_0/k_{el}, where k_{el} is the API elimination rate constant. With routes other than the intravenous, for such systems, AUC = $F \cdot D/Cl_T$, where F is the absolute bioavailability of the API.

Thus, in a further aspect, the present invention provides a process for modulating the bioavailability of an API when administered in its normal and effective dose range as a co-crystal, whereby the AUC is increased, the time to T_{max} is reduced, or C_{max} is increased, as compared to a reference form, which process comprises:

(1) grinding, heating or contacting in solution the API with a co-crystal forming compound under crystallization conditions, so as to form a co-crystal of the API and the co-crystal forming compound; and

(2) isolating co-crystals comprising the API and the co-crystal forming compound.

Examples of the above embodiments include: co-crystal compositions with a time to T_{max} that is reduced by at least 10% as compared to the reference form, co-crystal compositions with a time to T_{max} that is reduced by at least 20% over the reference form, co-crystal compositions with a time to T_{max} that is reduced by at least 40% over the reference form, co-crystal compositions with a time to T_{max} that is reduced by at least 50% over the reference form, co-crystal compositions with a T_{max} that is reduced by at least 60% over the reference form, co-crystal compositions with a T_{max} that is reduced by at least 70% over the reference form, co-crystal compositions with a T_{max} that is reduced by at least 80% over the reference form, co-crystal compositions with a T_{max} that is reduced by at least 90% over the reference form, co-crystal compositions with a C_{max} that is increased by at least 20% over the reference form, co-crystal compositions with a C_{max} that is increased by at least 30% over the reference form, co-crystal compositions with a C_{max} that is increased by at least 40% over the reference form, co-crystal compositions with a C_{max} that is increased by at least 50% over the reference form, co-crystal compositions with a C_{max} that is

increased by at least 60% over the reference form, co-crystal compositions with a C_{max} that is increased by at least 70% over the reference form, co-crystal compositions with a C_{max} that is increased by at least 80% over the reference form, co-crystal compositions with a Cmax that is increased by at least 2 fold, 3 fold, 5 fold, 7.5 fold, 10 fold, 25 fold, 50 fold or 100 fold, co-crystal compositions with an AUC that is increased by at least 10% over the reference form, co-crystal compositions with an AUC that is increased by at least 20% over the reference form, co-crystal compositions with an AUC that is increased by at least 30% over the reference form, co-crystal compositions with an AUC that is increased by at least 40% over the reference form, co-crystal compositions with an AUC that is increased by at least 50% over the reference form, co-crystal compositions with an AUC that is increased by at least 60% over the reference form, co-crystal compositions with an AUC that is increased by at least 70% over the reference form, co-crystal compositions with an AUC that is increased by at least 80% over the reference form or co-crystal compositions with an AUC that is increased by at least 2 fold, 3 fold, 4 fold, 5 fold, 6 fold, 7 fold, 8 fold, 9 fold, or 10 fold. Other examples include wherein the reference form is crystalline, wherein the reference form is amorphous, wherein the reference form is an anhydrous crystalline sodium salt, or wherein the reference form is an anhydrous crystalline HCl salt.

Dose Response Modulation

In a further aspect the present invention provides a process for improving the dose response of an API, which process comprises:

(1) contacting in solution an API with a co-crystal forming compound under crystallization conditions, so as to form a co-crystal of the API and the co-crystal forming compound; and

(2) isolating co-crystals comprising the API and the co-crystal forming compound.

Dose response is the quantitative relationship between the magnitude of response and the dose inducing the response and may be measured by conventional means known in the art. The curve relating effect (as the dependent variable) to dose (as the independent variable) for an API-cell system is the "dose-response curve". Typically, the dose-response curve is the measured response to an API plotted against

the dose of the API (mg/kg) given. The dose response curve can also be a curve of AUC against the dose of the API given.

In an embodiment of the present invention, a co-crystal of the present invention has an increased dose response curve or a more linear dose response curve than the corresponding reference compound.

Increased Stability

In a still further aspect the present invention provides a process for improving the stability of an API (as compared to a reference form such as its free form or a salt thereof), which process comprises:

(1) grinding, heating or contacting in solution the pharmaceutical salt with a co-crystal forming compound under crystallization conditions, so as to form a co-crystal of the API and the co-crystal forming compound; and

(2) isolating co-crystals comprising the API and the co-crystal forming compound.

In a preferred embodiment, the compositions of the present invention, including the API or active pharmaceutical ingredient (API) and formulations comprising the API, are suitably stable for pharmaceutical use. Preferably, the API or formulations thereof of the present invention are stable such that when stored at 30 degrees C for 2 years, less than 0.2 % of any one degradant is formed. The term degradant refers herein to product(s) of a single type of chemical reaction. For example, if a hydrolysis event occurs that cleaves a molecule into two products, for the purpose of the present invention, it would be considered a single degradant. More preferably, when stored at 40 degrees C for 2 years, less than 0.2 % of any one degradant is formed. Alternatively, when stored at 30 degrees C for 3 months, less than 0.2% or 0.15 %, or 0.1 % of any one degradant is formed, or when stored at 40 degrees C for 3 months, less than 0.2 % or 0.15 %, or 0.1 % of any one degradant is formed. Further alternatively, when stored at 60 degrees C for 4 weeks, less than 0.2 % or 0.15 %, or 0.1 % of any one degradant is formed. The relative humidity (RH) may be specified as ambient (RH), 75 % (RH), or as any single integer between 1 to 99 %.

Difficult to Salt or Unsaltable Compounds

In a still further aspect the present invention provides a process for making co-crystals of unsaltable or difficult to salt APIs which process comprises:

(1) grinding, heating or contacting in solution an API with a co-crystal forming compound under crystallization conditions, so as to form a co-crystal of the API and the co-crystal forming compound; and

(2) isolating co-crystals comprising the API and the co-crystal forming compound.

Difficult to salt compounds include bases with a pKa < 3 or acids with a pKa > 10. Zwitter ions are also difficult to salt or unsaltable compounds according to the present invention.

Decreasing Hygroscopicity

In a still further aspect, the present invention provides a method for decreasing the hygroscopicity of an API, which method comprises:

(1) grinding, heating or contacting in solution the API with a co-crystal forming compound under crystallization conditions, so as to form a co-crystal of the API and the co-crystal forming compound; and

(2) isolating co-crystals comprising the API and the co-crystal forming compound.

An aspect of the present invention provides a pharmaceutical composition comprising a co-crystal of an API that is less hygroscopic than amorphous or crystalline, free form or salt (including metal salts such as sodium, potassium, lithium, calcium, magnesium) or another reference compound. Hygroscopicity can be assessed by dynamic vapor sorption analysis, in which 5-50 mg of the compound is suspended from a Cahn microbalance. The compound being analyzed should be placed in a non-hygroscopic pan and its weight should be measured relative to an empty pan composed of identical material and having nearly identical size, shape, and weight. Ideally, platinum pans should be used. The pans should be suspended in a chamber through which a gas, such as air or nitrogen, having a controlled and known percent relative humidity (%RH) is flowed until eqilibrium criteria are met. Typical equilibrium criteria include weight changes of less than 0.01 % over 3 minutes at

constant humidity and temperature. The relative humidity should be measured for samples dried under dry nitrogen to constant weight (<0.01 % change in 3 minutes) at 40 degrees C unless doing so would de-solvate or otherwise convert the material to an amorphous compound. In one aspect, the hygroscopicity of a dried compound can be assessed by increasing the RH from 5 to 95 % in increments of 5 % RH and then decreasing the RH from 95 to 5 % in 5 % increments to generate a moisture sorption isotherm. The sample weight should be allowed to equilibrate between each change in % RH. If the compound deliquesces or becomes amorphous above 75 % RH, but below 95 % RH, the experiment should be repeated with a fresh sample and the relative humidity range for the cycling should be narrowed to 5-75 % RH or 10-75 % RH, instead of 5-95 %RH. If the sample cannot be dried prior to testing due to lack of form stability, than the sample should be studied using two complete humidity cycles of either 10-75 % RH or 5-95 % RH, and the results of the second cycle should be used if there is significant weight loss at the end of the first cycle.

Hygroscopicity can be defined using various parameters. For purposes of the present invention, a non-hygroscopic molecule should not gain or lose more than 1.0 %, or more preferably, 0.5 % weight at 25 degrees C when cycled between 10 and 75 % RH (relative humidity at 25 degrees C). The non-hygroscopic molecule more preferably should not gain or lose more than 1.0 %, or more preferably, 0.5 % weight when cycled between 5 and 95 % RH at 25 degrees C, or more than 0.25 % of its weight between 10 and 75 % RH. Most preferably, a non-hygroscopic molecule will not gain or lose more than 0.25 % of its weight when cycled between 5 and 95 % RH.

Alternatively, for purposes of the present invention, hygroscopicity can be defined using the parameters of Callaghan et al., "Equilibrium moisture content of pharmaceutical excipients", in Api Dev. Ind. Pharm., Vol. 8, pp. 335-369 (1982). Callaghan et al. classified the degree of hygroscopicity into four classes.

Class 1: Non-hygroscopic	Essentially no moisture increases occur at relative humidities below 90 %.
Class 2: Slightly hygroscopic	Essentially no moisture increases occur at relative humidities below 80%.

Class 3: Moderately hygroscopic	Moisture content does not increase more than 5 % after storage for 1 week at relative humidities below 60 %.
Class 4: Very hygroscopic	Moisture content increase may occur at relative humidities as low as 40 to 50 %.

Alternatively, for purposes of the present invention, hygroscopicity can be defined using the parameters of the European Pharmacopoeia Technical Guide (1999, p. 86) which has defined hygrospocity, based on the static method, after storage at 25 degrees C for 24 hours at 80 % RH:

Slightly hygroscopic: Increase in mass is less than 2 percent m/m and equal to or greater than 0.2 percent m/m.

Hygroscopic: Increase in mass is less than 15 percent m/m and equal to or greater than 0.2 percent m/m.

Very Hygroscopic: Increase in mass is equal to or greater than 15 percent m/m.

Deliquescent: Sufficient water is absorbed to form a liquid.

Co-crystals of the present invention can be set forth as being in Class 1, Class 2, or Class 3, or as being Slightly hygroscopic, Hygroscopic, or Very Hygroscopic. Co-crystals of the present invention can also be set forth based on their ability to reduce hygroscopicity. Thus, preferred co-crystals of the present invention are less hygroscopic than a reference compound. The reference compound can be specified as the API in free form (free acid, free base, hydrate, solvate, etc.) or salt (e.g., especially metal salts such as sodium, potassium, lithium, calcium, or magnesium). Further included in the present invention are co-crystals that do not gain or lose more than 1.0 % weight at 25 degrees C when cycled between 10 and 75 % RH, wherein the reference compound gains or loses more than 1.0 % weight under the same conditions. Further included in the present invention are co-crystals that do not gain

or lose more than 0.5 % weight at 25 degrees C when cycled between 10 and 75 % RH, wherein the reference compound gains or loses more than 0.5 % or more than 1.0 % weight under the same conditions. Further included in the present invention are co-crystals that do not gain or lose more than 1.0 % weight at 25 degrees C when cycled between 5 and 95 % RH, wherein the reference compound gains or loses more than 1.0 % weight under the same conditions. Further included in the present invention are co-crystals that do not gain or lose more than 0.5 % weight at 25 degrees C when cycled between 5 and 95 % RH, wherein the reference compound gains or loses more than 0.5 % or more than 1.0 % weight under the same conditions. Further included in the present invention are co-crystals that do not gain or lose more than 0.25 % weight at 25 degrees C when cycled between 5 and 95 % RH, wherein the reference compound gains or loses more than 0.5 % or more than 1.0 % weight under the same conditions.

Further included in the present invention are co-crystals that have a hygroscopicity (according to Callaghan et al.) that is at least one class lower than the reference compound or at least two classes lower than the reference compound. Included are a Class 1 co-crystal of a Class 2 reference compound, a Class 2 co-crystal of a Class 3 reference compound, a Class 3 co-crystal of a Class 4 reference compound, a Class 1 co-crystal of a Class 3 reference compound, a Class 1 co-crystal of a Class 4 reference compound, or a Class 2 co-crystal of a Class 4 reference compound.

Further included in the present invention are co-crystals that have a hygroscopicity (according to the European Pharmacopoeia Technical Guide) that is at least one class lower than the reference compound or at least two classes lower than the reference compound. Non-limiting examples include; a slightly hygroscopic co-crystal of a hygroscopic reference compound, a hygroscopic co-crystal of a very hygroscopic reference compound, a very hygroscopic co-crystal of a deliquescent reference compound, a slightly hygroscopic co-crystal of a very hygroscopic reference compound, a slightly hygroscopic co-crystal of a deliquescent reference compound, and a hygroscopic co-crystal of a deliquescent reference compound.

Crystallizing Amorphous Compounds

In a further aspect, the present invention provides a process for crystallizing an amorphous compound, which process comprises:

(1) grinding, heating or contacting in solution the API with a co-crystal forming compound under crystallization conditions, so as to form a co-crystal of the API and the co-crystal forming compound; and

(2) isolating co-crystals comprising the API and the co-crystal forming compound.

An amorphous compound includes compounds that do not crystallize using routine methods in the art.

Decreasing Form Diversity

In a still further embodiment aspect the present invention provides a process for reducing the form diversity of an API, which process comprises:

(1) grinding, heating or contacting in solution the API with a co-crystal forming compound under crystallization conditions, so as to form a co-crystal of the API and the co-crystal forming compound; and

(2) isolating co-crystals comprising the API and the co-crystal forming compound.

For purposes of the present invention, the number of forms of a co-crystal is compared to the number of forms of a reference compound (e.g. the free form or a salt of the API) that can be made using routine methods in the art.

Morphology Modulation

In a still further aspect the present invention provides a process for modifying the morphology of an API, which process comprises:

(1) grinding, heating or contacting in solution the API with a co-crystal forming compound under crystallization conditions, so as to form a co-crystal of the API and the co-crystal forming compound; and

(2) isolating co-crystals comprising the API and the co-crystal forming compound.

In an embodiment the co-crystal comprises or consists of a co-crystal former and a pharmaceutical wherein the interaction between the two, e.g., H-bonding, occurs between a functional group of Table III of an API with a corresponding

interacting group of Table III. In a further embodiment, the co-crystal comprises a co-crystal former of Table I or II and an API with a corresponding interacting group of Table III. In a further embodiment the co-crystal comprises an API from Table IV and a co-crystal former with a functional group of Table III. In a further embodiment, the co-crystal is from Table I or II. In an aspect of the invention, only co-crystals having an H-bond acceptor on the first molecule and an H-bond donor on the second molecule, where the first and second molecules are either co-crystal former and API respectively or API and co-crystal former respectively, are included in the present invention. Table IV includes the CAS number, chemical name or a PCT or patent reference (each incorporated herein in their entireties). Thus, whether a particular API contains an H-bond donor, acceptor or both is readily apparent.

In another embodiment, the co-crystal former and API each have only one H-bond donor/acceptor. In another aspect, the molecular weight of the API is less than 2000, 1500, 1000, 750, 500, 350, 200, or 150 Daltons. In another embodiment, the molecular weight of the API is between 100-200, 200-300, 300-400, 400-500, 500-600, 600-700, 700-800, 800-900, 900-1000, 1000-1200, 1200-1400, 1400-1600, 1600-1800, or 1800-2000. APIs with the above molecular weights may also be specifically excluded from the present invention.

In another embodiment, peptides, proteins, nucleic acids or other biological APIs are excluded from the present invention. In another embodiment, all non-pharmaceutically acceptable co-crystal formers are excluded from the present invention. In another embodiment, organometalic APIs are excluded from the present invention. In another embodiment, a co-crystal former comprising any one or more of the functional groups of Table III may be specifically excluded from the present invention. In another embodiment, any one or more of the co-crystal formers of Table I or II may be specifically excluded from the present invention. Any APIs currently known in the art may also be specifically excluded from the present invention. For example, carbanazepine, itraconazole, nabumetone, fluoxetine, acetaminophen and theophylline can each be specifically excluded from the present invention. In another embodiment, the API is not a salt, is not a non-metal salt, or is not a metal salt, e.g., sodium, potassium, lithium, calcium or magnesium. In another embodiment, the API is a salt, is a non-metal salt, or is a metal salt, e.g., sodium, potassium, lithium, calcium, magnesium. In one embodiment, the API does not contain a halogen. In one embodiment, the API does contain a halogen.

In another embodiment, any one or more of the APIs of Table IV may be specifically excluded from the present invention. Any APIs currently known in the art may also be specifically excluded from the present invention. For example, nabumetone:2,3-naphthalenediol, fluoxetine HCl:benzoic acid, fluoxetine HCl:succinic acid, acetaminophen:piperazine, acetaminophen:theophylline, theophylline:salicylic acid, theophylline:p-hydroxybenzoic acid, theophylline:sorbic acid, theophylline:1-hydroxy-2-naphthoic acid, theophylline:glycolic acid, theophylline:2,5-dihydroxybenzoic acid, theophylline:chloroacetic acid, bis(diphenylhydantoin):9-ethyladenine acetylacetone solvate, bis(diphenylhydantoin):9-ethyladenine 2,4-pentanedione solvate, 5,5-diphenylbarbituric acid:9-ethyladenine, bis(diphenylhydantoin):9-ethyladenine, 4-aminobenzoic acid:4-aminobenzonitrile, sulfadimidine:salicylic acid, 8-hydroxyquinolinium 4-nitrobenzoate:4-nitrobenzoic acid, sulfaproxyline:caffeine, retro-inverso-isopropyl (2R,3S)-4-cyclohexyl-2-hydroxy-3-(N-((2R)-2-morpholinocarbonylmethyl-3-(1-naphthyl)propionyl)-L-histidylamino)butyrate:cinnamic acid monohydrate, benzoic acid:isonicotinamide, 3-(2-N',N'-(dimethylhydrazino)-4-thiazolylmethylthio)-N''-sulfamoylpropionamidine:maleic acid, diglycine hydrochloride ($C_2H_5NO_2$:$C_2H_6NO_2^+Cl^-$), octadecanoic acid:3-pyridinecarboxamide, cis-N-(3-methyl-1-(2-(1,2,3,4-tetrahydro)naphthyl)-piperidin-4-yl)-N-phenylpropanamide hydrochloride:oxalic acid, trans-N-(3-methyl-1-(2-(1,2,3,4-tetrahydro)naphthyl)-piperidin-4-ylium)-N-phenylpropanamide oxalate:oxalic acid dihydrate, bis(1-(3-((4-(2-isopropoxyphenyl)-1-piperazinyl)methyl)benzoyl)piperidine) succinate:succinic acid, bis(p-cyanophenyl)imidazolylmethane:succinic acid, cis-1-((4-(1-imidazolylmethyl)cyclohexyl)methyl)imidazole:succinic acid, (+)-2-(5,6-dimethoxy-1,2,3,4-tetrahydro-1-naphthyl)imidazoline:(+)-dibenzoyl-D-tartaric acid, raclopride:tartaric acid, 2,6-diamino-9-ethylpurine:5,5-diethylbarbituric acid, 5,5-diethylbarbituric acid:bis(2-aminopyridine), 5,5-diethylbarbituric acid:acetamide, 5,5-diethylbarbituric acid:KI_3, 5,5-diethylbarbituric acid:urea, bis(barbital):hexamethylphosphoramide, 5,5-diethylbarbituric acid:imidazole, barbital:1-methylimidazole, 5,5-diethylbarbituric acid:N-methyl-2-pyridone, 2,4-diamino-5-(3,4,5-trimethoxybenzyl)-pyrimidine:5,5-diethylbarbituric acid, bis(barbital):caffeine, bis(barbital):1-methylimidazole, bis(beta-cyclodextrin):bis(barbital) hydrate, tetrakis(beta-cyclodextrin):tetrakis(barbital), 9-

ethyladenine:5,5-diethylbarbituric acid, barbital:N'-(p-cyanophenyl)-N-(p-iodophenyl)melamine, barbital:2-amino-4-(m-bromophenylamino)-6-chloro-1,3,5-triazine, 5,5-diethylbarbituric acid:N,N'-diphenylmelamine, 5,5-diethylbarbituric acid:N,N'-bis(p-chlorophenyl)melamine, N,N'-bis(p-bromophenyl)melamine:5,5-diethylbarbituric acid, 5,5-diethylbarbituric acid:N,N'-bis(p-iodophenyl)melamine, 5,5-diethylbarbituric acid:N,N'-bis(p-tolyl)melamine, 5,5-diethylbarbituric acid:N,N'-bis(m-tolyl)melamine, 5,5-diethylbarbituric acid:N,N'-bis(m-chlorophenyl)melamine, N,N'-Bis(m-methylphenyl)melamine:barbital, N,N'-bis(m-chlorophenyl)melamine:barbital tetrahydrofuran solvate, 5,5-diethylbarbituric acid:N,N'-bis(t-butyl)melamine, 5,5-diethylbarbituric acid:N,N'-di(t-butyl)melamine, 6,6'-diquinolyl ether:5,5-diethylbarbituric acid, 5-t-butyl-2,4,6-triaminopyrimidine:diethylbarbituric acid, N,N'-bis(4-carboxymethylphenyl)melamine:barbital ethanol solvate, N,N'-bis(4-t-butylphenyl)melamine:barbital, tris(5,17-N,N'-bis(4-amino-6-(butylamino)-1,3,5-triazin-2-yl)diamino-11,23-dinitro-25,26,27,28-tetrapropoxycalix(4)arene):hexakis(diethylbarbituric acid) toluene solvate, N,N'-bis(m-fluorophenyl)melamine:barbital, N,N'-bis(m-bromophenyl)melamine:barbital acetone solvate, N,N'-bis(m-iodophenyl)melamine:barbital acetonitrile solvate, N,N'-bis(m-trifluoromethylphenyl)melamine:barbital acetonitrile solvate, aminopyrine:barbital, N,N'-bis(4-fluorophenyl)melamine:barbital, N,N'-bis(4-trifluoromethylphenyl)melamine:barbital, 2,4-diamino-5-(3,4,5-trimethoxybenzyl)pyrimidine:barbital, hydroxybutyrate:hydroxyvalerate, 2-aminopyrimidine:succinic acid, 1,3-bis(((6-methylpyrid-2-yl)amino)carbonyl)benzene:glutaric acid, 5-t-butyl-2,4,6-triaminopyrimidine:diethylbarbituric acid, bis(dithiobiuret-S,S')nickel(II):diuracil, platinum 3,3'-dihydroxymethyl-2,2'-bipyridine dichloride:AgF_3CSO_3, 4,4'-bipyridyl:isophthalic acid, 4,4'-bipyridyl:1,4-naphthalenedicarboxylic acid, 4,4'-bipyridyl:1,3,5-cyclohexane-tricarboxylic acid, 4,4'-bipyridyl:tricaballylic acid, urotropin:azelaic acid, insulin:C8-HI (octanoyl-N^{ε}-LysB29-human insulin), isonicotinamide:cinnamic acid, isonicotinamide:3-hydroxybenzoic acid, isonicotinamide:3-N,N-dimethylaminobenzoic acid, isonicotinamide:3,5-bis(trifluoromethyl)-benzoic acid, isonicotinamide:d,l-mandelic acid, isonicotinamide:chloroacetic acid, isonicotinamide:fumaric acid monoethyl ester, isonicotinamide:12-bromododecanoic acid, isonicotinamide:fumaric acid,

isonicotinamide:succinic acid, isonicotinamide:4-ketopimelic acid, isonicotinamide:thiodiglycolic acid, 1,3,5-cyclohexane-tricarboxylic acid:hexamethyltetramine, 1,3,5-cyclohexane-tricarboxylic acid:4,7-phenanthroline, 4,7-phenanthroline:oxalic acid, 4,7-phenanthroline:terephthalic acid, 4,7-phenanthroline: 1,3,5-cyclohexane-tricarboxylic acid, 4,7-phenanthroline:1,4-naphthalenedicarboxylic acid, pyrazine:methanoic acid, pyrazine:ethanoic acid, pyrazine:propanoic acid, pyrazine:butanoic acid, pyrazine:pentanoic acid, pyrazine:hexanoic acid, pyrazine:heptanoic acid, pyrazine:octanoic acid, pyrazine:nonanoic acid, pyrazine:decanoic acid, diammine-(deoxy-quanyl-quanyl-N^7,N^7)-platinum:tris(glycine) hydrate, 2-aminopyrimidine:p-phenylenediacetic acid, bis(2-aminopyrimidin-1-ium)fumarate:fumaric acid, 2-aminopyrimidine:indole-3-acetic acid, 2-aminopyrimidine:N-methylpyrrole-2-carboxylic acid, 2-aminopyrimidine:thiophen-2-carboxylic acid, 2-aminopyrimidine:(+)-camphoric acid, 2,4,6-Trinitrobenzoic acid: 2-aminopyrimidine, 2-aminopyrimidine:4-aminobenzoic acid, 2-aminopyrimidine:bis(phenoxyacetic acid), 2-aminopyrimidine:(2,4-dichlorophenoxy)acetic acid, 2-aminopyrimidine:(3,4-dichlorophenoxy)acetic acid, 2-aminopyrimidine:indole-2-carboxylic acid, 2-aminopyrimidine:terephthalic acid, 2-aminopyrimidine:bis(2-nitrobenzoic acid), 2-aminopyrimidine:bis(2-aminobenzoic acid), 2-aminopyrimidine:3-aminobenzoic acid, 2-hexeneoic acid:isonicotinamide, 4-nitrobenzoic acid:isonicotinamide, 3,5-dinitrobenzoic acid:isonicotinamide:4-methylbenzoic acid, 2-amino-5-nitropyrimidine:2-amino-3-nitropyridine, 3,5-dinitrobenzoic acid:4-chlorobenzamide, 3-dimethylaminobenzoic acid4-chlorobenzamide, fumaric acid:4-chlorobenzamide, oxine:4-nitrobenzoic acid, oxine:3,5-dinitrobenzoic acid, oxine:3,5-dinitrosalicylic acid, 3-[2-(N',N'-dimethylhydrazino)-4-thiazolylmethylthio]-N^2-sulfamoylpropionamidine:maleic acid, 5-fluorouracil:9-ethylhypoxanthine, 5-fluorouracil:cytosine dihydrate, 5-fluorouracil:theophylline monohydrate, stearic acid:nicotinamide, cis-1-{[4-(1-imidazolylmethyl)cyclohexyl]methyl}imidazole:succinic acid, CGS18320B:succinic acid, sulfaproxyline:caffeine, 4-aminobenzoic acid:4-aminobenzonitrile, 3,5-dinitrobenzoic acid:isonicotinamide:3-methylbenzoic acid, 3,5-dinitrobenzoic acid:isonicotinamide:4-(dimethylamino)benzoic acid, 3,5-dinitrobenzoic acid:isonicotinamide:4-hydroxy-3-methoxycinnamic acid, isonicotinamide:oxalic acid, isonicotinamide:malonic acid, isonicotinamide:succinic acid, isonicotinamide:glutaric acid, isonicotinamide:adipic acid, benzoic

acid:isonicotinamide, mazapertine:succinate, betaine:dichloronitrophenol, betainepyridine:dichloronitrophenol, betainepyridine:pentachlorophenol, 4-{2-[1-(2-hydroxyethyl)-4-pyridylidene]-ethylidene}-cyclo-hexa-2,5-dien-1-one:methyl 2,4-dihydroxybenzoate, 4-{2-[1-(2-hydroxyethyl)-4-pyridylidene]-ethylidene}-cyclo-hexa-2,5-dien-1-one:2,4-dihydroxypropiophenone, 4-{2-[1-(2-hydroxyethyl)-4-pyridylidene]-ethylidene}-cyclo-hexa-2,5-dien-1-one:2,4-dihydroxyacetophenone, squaric acid:4,4'-dipyridylacetylene, squaric acid:1,2-bis(4-pyridyl)ethylene, chloranilic acid:1,4-bis[(4-pyridyl)ethynyl]benzene, 4,4'-bipyridine:phthalic acid, 4,4'-dipyridylacetylene:phthalic acid, bis(pentamethylcyclopentadienyl)iron:bromanilic acid, bis(pentamethylcyclopentadienyl)iron:chloranilic acid, bis(pentamethylcyclopentadienyl)iron:cyananilic acid, pyrazinotetrathiafulvalene:chloranilic acid, phenol:pentafluorophenol, co-crystals of itraconazole, and co-crystals of topiramate are specifically excluded from the present invention.

Excipients employed in pharmaceutical compositions of the present invention can be solids, semi-solids, liquids or combinations thereof. Preferably, excipients are solids. Compositions of the invention containing excipients can be prepared by any known technique of pharmacy that comprises admixing an excipient with an API or therapeutic agent. A pharmaceutical composition of the invention contains a desired amount of API per dose unit and, if intended for oral administration, can be in the form, for example, of a tablet, a caplet, a pill, a hard or soft capsule, a lozenge, a cachet, a dispensable powder, granules, a suspension, an elixir, a dispersion, a liquid, or any other form reasonably adapted for such administration. If intended for parenteral administration, it can be in the form, for example, of a suspension or transdermal patch. If intended for rectal administration, it can be in the form, for example, of a suppository. Presently preferred are oral dosage forms that are discrete dose units each containing a predetermined amount of the API, such as tablets or capsules.

In another embodiment, APIs with an inappropriate pH for transdermal patches can be co-crystallized with an appropriate co-crystal former, thereby adjusting its pH to an appropriate level for use as a transdermal patch. In another embodiment, an APIs pH level can be optimized for use in a transdermal patch via co-crystallization with an appropriate co-crystal former.

Non-limiting examples follow of excipients that can be used to prepare pharmaceutical compositions of the invention.

Pharmaceutical compositions of the invention optionally comprise one or more pharmaceutically acceptable carriers or diluents as excipients. Suitable carriers or diluents illustratively include, but are not limited to, either individually or in combination, lactose, including anhydrous lactose and lactose monohydrate; starches, including directly compressible starch and hydrolyzed starches (e.g., Celutab™ and Emdex™); mannitol; sorbitol; xylitol; dextrose (e.g., Cerelose™ 2000) and dextrose monohydrate; dibasic calcium phosphate dihydrate; sucrose-based diluents; confectioner's sugar; monobasic calcium sulfate monohydrate; calcium sulfate dihydrate; granular calcium lactate trihydrate; dextrates; inositol; hydrolyzed cereal solids; amylose; celluloses including microcrystalline cellulose, food grade sources of alpha- and amorphous cellulose (e.g., RexcelJ), powdered cellulose, hydroxypropylcellulose (HPC) and hydroxypropylmethylcellulose (HPMC); calcium carbonate; glycine; bentonite; block co-polymers; polyvinylpyrrolidone; and the like. Such carriers or diluents, if present, constitute in total about 5% to about 99%, preferably about 10% to about 85%, and more preferably about 20% to about 80%, of the total weight of the composition. The carrier, carriers, diluent, or diluents selected preferably exhibit suitable flow properties and, where tablets are desired, compressibility.

Lactose, mannitol, dibasic sodium phosphate, and microcrystalline cellulose (particularly Avicel PH microcrystalline cellulose such as Avicel PH 101), either individually or in combination, are preferred diluents. These diluents are chemically compatible with many co-crystals described herein. The use of extragranular microcrystalline cellulose (that is, microcrystalline cellulose added to a granulated composition) can be used to improve hardness (for tablets) and/or disintegration time. Lactose, especially lactose monohydrate, is particularly preferred. Lactose typically provides compositions having suitable release rates of co-crystals, stability, pre-compression flowability, and/or drying properties at a relatively low diluent cost. It provides a high density substrate that aids densification during granulation (where wet granulation is employed) and therefore improves blend flow properties and tablet properties.

Pharmaceutical compositions of the invention optionally comprise one or more pharmaceutically acceptable disintegrants as excipients, particularly for tablet

formulations. Suitable disintegrants include, but are not limited to, either individually or in combination, starches, including sodium starch glycolate (e.g., Explotab™ of PenWest) and pregelatinized corn starches (e.g., National™ 1551 of National Starch and Chemical Company, National™ 1550, and Colorcon™ 1500), clays (e.g., Veegum™ HV of R.T. Vanderbilt), celluloses such as purified cellulose, microcrystalline cellulose, methylcellulose, carboxymethylcellulose and sodium carboxymethylcellulose, croscarmellose sodium (e.g., Ac-Di-Sol™ of FMC), alginates, crospovidone, and gums such as agar, guar, locust bean, karaya, pectin and tragacanth gums.

Disintegrants may be added at any suitable step during the preparation of the composition, particularly prior to granulation or during a lubrication step prior to compression. Such disintegrants, if present, constitute in total about 0.2% to about 30%, preferably about 0.2% to about 10%, and more preferably about 0.2% to about 5%, of the total weight of the composition.

Croscarmellose sodium is a preferred disintegrant for tablet or capsule disintegration, and, if present, preferably constitutes about 0.2% to about 10%, more preferably about 0.2% to about 7%, and still more preferably about 0.2% to about 5%, of the total weight of the composition. Croscarmellose sodium confers superior intragranular disintegration capabilities to granulated pharmaceutical compositions of the present invention.

Pharmaceutical compositions of the invention optionally comprise one or more pharmaceutically acceptable binding agents or adhesives as excipients, particularly for tablet formulations. Such binding agents and adhesives preferably impart sufficient cohesion to the powder being tableted to allow for normal processing operations such as sizing, lubrication, compression and packaging, but still allow the tablet to disintegrate and the composition to be absorbed upon ingestion. Such binding agents may also prevent or inhibit crystallization or recrystallization of a co-crsytal of the present invention once the salt has been dissolved in a solution. Suitable binding agents and adhesives include, but are not limited to, either individually or in combination, acacia; tragacanth; sucrose; gelatin; glucose; starches such as, but not limited to, pregelatinized starches (e.g., National™ 1511 and National™ 1500); celluloses such as, but not limited to, methylcellulose and carmellose sodium (e.g., Tylose™); alginic acid and salts of alginic acid; magnesium aluminum silicate; PEG; guar gum; polysaccharide acids; bentonites; povidone, for example povidone K-15,

K-30 and K-29/32; polymethacrylates; HPMC; hydroxypropylcellulose (e.g., Klucel™ of Aqualon); and ethylcellulose (e.g., Ethocel™ of the Dow Chemical Company). Such binding agents and/or adhesives, if present, constitute in total about 0.5% to about 25%, preferably about 0.75% to about 15%, and more preferably about 1% to about 10%, of the total weight of the pharmaceutical composition.

Many of the binding agents are polymers comprising amide, ester, ether, alcohol or ketone groups and, as such, are preferably included in pharmaceutical compositions of the present invention. Polyvinylpyrrolidones such as povidone K-30 are especially preferred. Polymeric binding agents can have varying molecular weight, degrees of crosslinking, and grades of polymer. Polymeric binding agents can also be copolymers, such as block co-polymers that contain mixtures of ethylene oxide and propylene oxide units. Variation in these units' ratios in a given polymer affects properties and performance. Examples of block co-polymers with varying compositions of block units are Poloxamer 188 and Poloxamer 237 (BASF Corporation).

Pharmaceutical compositions of the invention optionally comprise one or more pharmaceutically acceptable wetting agents as excipients. Such wetting agents are preferably selected to maintain the co-crystal in close association with water, a condition that is believed to improve bioavailability of the composition. Such wetting agents can also be useful in solubilizing or increasing the solubility of co-crystals.

Non-limiting examples of surfactants that can be used as wetting agents in pharmaceutical compositions of the invention include quaternary ammonium compounds, for example benzalkonium chloride, benzethonium chloride and cetylpyridinium chloride, dioctyl sodium sulfosuccinate, polyoxyethylene alkylphenyl ethers, for example nonoxynol 9, nonoxynol 10, and degrees Ctoxynol 9, poloxamers (polyoxyethylene and polyoxypropylene block copolymers), polyoxyethylene fatty acid glycerides and oils, for example polyoxyethylene (8) caprylic/capric mono- and diglycerides (e.g., Labrasol™ of Gattefosse), polyoxyethylene (35) castor oil and polyoxyethylene (40) hydrogenated castor oil; polyoxyethylene alkyl ethers, for example polyoxyethylene (20) cetostearyl ether, polyoxyethylene fatty acid esters, for example polyoxyethylene (40) stearate, polyoxyethylene sorbitan esters, for example polysorbate 20 and polysorbate 80 (e.g., Tween™ 80 of ICI), propylene glycol fatty acid esters, for example propylene glycol laurate (e.g., Lauroglycol™ of Gattefosse), sodium lauryl sulfate, fatty acids and salts thereof, for example oleic acid, sodium

oleate and triethanolamine oleate, glyceryl fatty acid esters, for example glyceryl monostearate, sorbitan esters, for example sorbitan monolaurate, sorbitan monooleate, sorbitan monopalmitate and sorbitan monostearate, tyloxapol, and mixtures thereof. Such wetting agents, if present, constitute in total about 0.25% to about 15%, preferably about 0.4% to about 10%, and more preferably about 0.5% to about 5%, of the total weight of the pharmaceutical composition.

Wetting agents that are anionic surfactants are preferred. Sodium lauryl sulfate is a particularly preferred wetting agent. Sodium lauryl sulfate, if present, constitutes about 0.25% to about 7%, more preferably about 0.4% to about 4%, and still more preferably about 0.5% to about 2%, of the total weight of the pharmaceutical composition.

Pharmaceutical compositions of the invention optionally comprise one or more pharmaceutically acceptable lubricants (including anti-adherents and/or glidants) as excipients. Suitable lubricants include, but are not limited to, either individually or in combination, glyceryl behapate (e.g., Compritol™ 888 of Gattefosse); stearic acid and salts thereof, including magnesium, calcium and sodium stearates; hydrogenated vegetable oils (e.g., Sterotex™ of Abitec); colloidal silica; talc; waxes; boric acid; sodium benzoate; sodium acetate; sodium fumarate; sodium chloride; DL-leucine; PEG (e.g., Carbowax™ 4000 and Carbowax™ 6000 of the Dow Chemical Company); sodium oleate; sodium lauryl sulfate; and magnesium lauryl sulfate. Such lubricants, if present, constitute in total about 0. 1% to about 10%, preferably about 0.2% to about 8%, and more preferably about 0.25% to about 5%, of the total weight of the pharmaceutical composition.

Magnesium stearate is a preferred lubricant used, for example, to reduce friction between the equipment and granulated mixture during compression of tablet formulations.

Suitable anti-adherents include, but are not limited to, talc, cornstarch, DL-leucine, sodium lauryl sulfate and metallic stearates. Talc is a preferred anti-adherent or glidant used, for example, to reduce formulation sticking to equipment surfaces and also to reduce static in the blend. Talc, if present, constitutes about 0.1% to about 10%, more preferably about 0.25% to about 5%, and still more preferably about 0.5% to about 2%, of the total weight of the pharmaceutical composition.

Glidants can be used to promote powder flow of a solid formulation. Suitable glidants include, but are not limited to, colloidal silicon dioxide, starch, talc, tribasic

calcium phosphate, powdered cellulose and magnesium trisilicate. Colloidal silicon dioxide is particularly preferred.

Other excipients such as colorants, flavors and sweeteners are known in the pharmaceutical art and can be used in pharmaceutical compositions of the present invention. Tablets can be coated, for example with an enteric coating, or uncoated. Compositions of the invention can further comprise, for example, buffering agents.

Optionally, one or more effervescent agents can be used as disintegrants and/or to enhance organoleptic properties of pharmaceutical compositions of the invention. When present in pharmaceutical compositions of the invention to promote dosage form disintegration, one or more effervescent agents are preferably present in a total amount of about 30% to about 75%, and preferably about 45% to about 70%, for example about 60%, by weight of the pharmaceutical composition.

According to a particularly preferred embodiment of the invention, an effervescent agent, present in a solid dosage form in an amount less than that effective to promote disintegration of the dosage form, provides improved dispersion of the API in an aqueous medium. Without being bound by theory, it is believed that the effervescent agent is effective to accelerate dispersion of the API from the dosage form in the gastrointestinal tract, thereby further enhancing absorption and rapid onset of therapeutic effect. When present in a pharmaceutical composition of the invention to promote intragastrointestinal dispersion but not to enhance disintegration, an effervescent agent is preferably present in an amount of about 1% to about 20%, more preferably about 2.5% to about 15%, and still more preferably about 5% to about 10%, by weight of the pharmaceutical composition.

An "effervescent agent" herein is an agent comprising one or more compounds which, acting together or individually, evolve a gas on contact with water. The gas evolved is generally oxygen or, most commonly, carbon dioxide. Preferred effervescent agents comprise an acid and a base that react in the presence of water to generate carbon dioxide gas. Preferably, the base comprises an alkali metal or alkaline earth metal carbonate or bicarbonate and the acid comprises an aliphatic carboxylic acid.

Non-limiting examples of suitable bases as components of effervescent agents useful in the invention include carbonate salts (e.g., calcium carbonate), bicarbonate salts (e.g., sodium bicarbonate), sesquicarbonate salts, and mixtures thereof. Calcium carbonate is a preferred base.

Non-limiting examples of suitable acids as components of effervescent agents and/or solid organic acids useful in the invention include citric acid, tartaric acid (as D-, L-, or D/L-tartaric acid), malic acid (as D-, L-, or DL-malic acid), maleic acid, fumaric acid, adipic acid, succinic acid, acid anhydrides of such acids, acid salts of such acids, and mixtures thereof. Citric acid is a preferred acid.

In a preferred embodiment of the invention, where the effervescent agent comprises an acid and a base, the weight ratio of the acid to the base is about 1:100 to about 100:1, more preferably about 1:50 to about 50:1, and still more preferably about 1:10 to about 10:1. In a further preferred embodiment of the invention, where the effervescent agent comprises an acid and a base, the ratio of the acid to the base is approximately stoichiometric.

Excipients which solubilize APIs typically have both hydrophilic and hydrophobic regions, or are preferably amphiphilic or have amphiphilic regions. One type of amphiphilic or partially-amphiphilic excipient comprises an amphiphilic polymer or is an amphiphilic polymer. A specific amphiphilic polymer is a polyalkylene glycol, which is commonly comprised of ethylene glycol and/or propylene glycol subunits. Such polyalkylene glycols can be esterified at their termini by a carboxylic acid, ester, acid anhyride or other suitable moiety. Examples of such excipients include poloxamers (symmetric block copolymers of ethylene glycol and propylene glycol; e.g., poloxamer 237), polyalkyene glycolated esters of tocopherol (including esters formed from a di- or multi-functional carboxylic acid; e.g., d-alpha-tocopherol polyethylene glycol-1000 succinate), and macrogolglycerides (formed by alcoholysis of an oil and esterification of a polyalkylene glycol to produce a mixture of mono-, di- and tri-glycerides and mono- and di-esters; e.g., stearoyl macrogol-32 glycerides). Such pharmaceutical compositions are advantageously administered orally.

Pharmaceutical compositions of the present invention can comprise about 10 % to about 50 %, about 25 % to about 50 %, about 30 % to about 45 %, or about 30 % to about 35 % by weight of a co-crystal; about 10 % to about 50 %, about 25 % to about 50 %, about 30 % to about 45 %, or about 30 % to about 35 % by weight of an excipient which inhibits crystallization in aqueous solution, in simulated gastric fluid, or in simulated intestinal fluid; and about 5 % to about 50 %, about 10 % to about 40 %, about 15 % to about 35 %, or about 30 % to about 35 % by weight of a binding

agent. In one example, the weight ratio of the co-crystal to the excipient which inhibits crystallization to binding agent is about 1 to 1 to 1.

Solid dosage forms of the invention can be prepared by any suitable process, not limited to processes described herein.

An illustrative process comprises (a) a step of blending an API of the invention with one or more excipients to form a blend, and (b) a step of tableting or encapsulating the blend to form tablets or capsules, respectively.

In a preferred process, solid dosage forms are prepared by a process comprising (a) a step of blending a co-crystal of the invention with one or more excipients to form a blend, (b) a step of granulating the blend to form a granulate, and (c) a step of tableting or encapsulating the blend to form tablets or capsules respectively. Step (b) can be accomplished by any dry or wet granulation technique known in the art, but is preferably a dry granulation step. A salt of the present invention is advantageously granulated to form particles of about 1 micrometer to about 100 micrometer, about 5 micrometer to about 50 micrometer, or about 10 micrometer to about 25 micrometer. One or more diluents, one or more disintegrants and one or more binding agents are preferably added, for example in the blending step, a wetting agent can optionally be added, for example in the granulating step, and one or more disintegrants are preferably added after granulating but before tableting or encapsulating. A lubricant is preferably added before tableting. Blending and granulating can be performed independently under low or high shear. A process is preferably selected that forms a granulate that is uniform in API content, that readily disintegrates, that flows with sufficient ease so that weight variation can be reliably controlled during capsule filling or tableting, and that is dense enough in bulk so that a batch can be processed in the selected equipment and individual doses fit into the specified capsules or tablet dies.

In an alternative embodiment, solid dosage forms are prepared by a process that includes a spray drying step, wherein an API is suspended with one or more excipients in one or more sprayable liquids, preferably a non-protic (e.g., non-aqueous or non-alcoholic) sprayable liquid, and then is rapidly spray dried over a current of warm air.

A granulate or spray dried powder resulting from any of the above illustrative processes can be compressed or molded to prepare tablets or encapsulated to prepare capsules. Conventional tableting and encapsulation techniques known in the art can

be employed. Where coated tablets are desired, conventional coating techniques are suitable.

Excipients for tablet compositions of the invention are preferably selected to provide a disintegration time of less than about 30 minutes, preferably about 25 minutes or less, more preferably about 20 minutes or less, and still more preferably about 15 minutes or less, in a standard disintegration assay.

Pharmaceutically acceptable co-crystals can be administered by controlled- or delayed-release means. Controlled-release pharmaceutical products have a common goal of improving drug therapy over that achieved by their non-controlled release counterparts. Ideally, the use of an optimally designed controlled-release preparation in medical treatment is characterized by a minimum of drug substance being employed to cure or control the condition in a minimum amount of time. Advantages of controlled-release formulations include: 1) extended activity of the drug; 2) reduced dosage frequency; 3) increased patient compliance; 4) usage of less total drug; 5) reduction in local or systemic side effects; 6) minimization of drug accumulation; 7) reduction in blood level fluctuations; 8) improvement in efficacy of treatment; 9) reduction of potentiation or loss of drug activity; and 10) improvement in speed of control of diseases or conditions. Kim, Cherng-ju, Controlled Release Dosage Form Design, 2 (Technomic Publishing, Lancaster, Pa.: 2000).

Conventional dosage forms generally provide rapid or immediate drug release from the formulation. Depending on the pharmacology and pharmacokinetics of the drug, use of conventional dosage forms can lead to wide fluctuations in the concentrations of the drug in a patient's blood and other tissues. These fluctuations can impact a number of parameters, such as dose frequency, onset of action, duration of efficacy, maintenance of therapeutic blood levels, toxicity, side effects, and the like. Advantageously, controlled-release formulations can be used to control a drug's onset of action, duration of action, plasma levels within the therapeutic window, and peak blood levels. In particular, controlled- or extended-release dosage forms or formulations can be used to ensure that the maximum effectiveness of a drug is achieved while minimizing potential adverse effects and safety concerns, which can occur both from under dosing a drug (i.e., going below the minimum therapeutic levels) as well as exceeding the toxicity level for the drug.

Most controlled-release formulations are designed to initially release an amount of drug (active ingredient) that promptly produces the desired therapeutic

effect, and gradually and continually release other amounts of drug to maintain this level of therapeutic or prophylactic effect over an extended period of time. In order to maintain this constant level of drug in the body, the drug must be released from the dosage form at a rate that will replace the amount of drug being metabolized and excreted from the body. Controlled-release of an active ingredient can be stimulated by various conditions including, but not limited to, pH, ionic strength, osmotic pressure, temperature, enzymes, water, and other physiological conditions or compounds.

A variety of known controlled- or extended-release dosage forms, formulations, and devices can be adapted for use with the co-crystals and compositions of the invention. Examples include, but are not limited to, those described in U.S. Pat. Nos.: 3,845,770; 3,916,899; 3,536,809; 3,598,123; 4,008,719; 5,674,533; 5,059,595; 5,591,767; 5,120,548; 5,073,543; 5,639,476; 5,354,556; 5,733,566; and 6,365,185 B1; each of which is incorporated herein by reference. These dosage forms can be used to provide slow or controlled-release of one or more active ingredients using, for example, hydroxypropylmethyl cellulose, other polymer matrices, gels, permeable membranes, osmotic systems (such as OROS® (Alza Corporation, Mountain View, Calif. USA)), multilayer coatings, microparticles, liposomes, or microspheres or a combination thereof to provide the desired release profile in varying proportions. Additionally, ion exchange materials can be used to prepare immobilized, adsorbed co-crystals and thus effect controlled delivery of the drug. Examples of specific anion exchangers include, but are not limited to, Duolite® A568 and Duolite® AP143 (Rohm & Haas, Spring House, PA. USA).

One embodiment of the invention encompasses a unit dosage form which comprises a pharmaceutically acceptable co-crystal, or a solvate, hydrate, dehydrate, anhydrous, or amorphous form thereof, and one or more pharmaceutically acceptable excipients or diluents, wherein the pharmaceutical composition or dosage form is formulated for controlled-release. Specific dosage forms utilize an osmotic drug delivery system.

A particular and well-known osmotic drug delivery system is referred to as OROS® (Alza Corporation, Mountain View, Calif. USA). This technology can readily be adapted for the delivery of compounds and compositions of the invention. Various aspects of the technology are disclosed in U.S. Pat. Nos. 6,375,978 B1;

6,368,626 B1; 6,342,249 B1; 6,333,050 B2; 6,287,295 B1; 6,283,953 B1; 6,270,787 B1; 6,245,357 B1; and 6,132,420; each of which is incorporated herein by reference.

Specific adaptations of OROS® that can be used to administer compounds and compositions of the invention include, but are not limited to, the OROS® Push-Pull™, Delayed Push-Pull™, Multi-Layer Push-Pull™, and Push-Stick™ Systems, all of which are well known. See, e.g., http://www.alza.com. Additional OROS® systems that can be used for the controlled oral delivery of compounds and compositions of the invention include OROS®-CT and L-OROS®. Id.; see also, Delivery Times, vol. II, issue II (Alza Corporation).

Conventional OROS® oral dosage forms are made by compressing a drug powder (e.g. co-crystal) into a hard tablet, coating the tablet with cellulose derivatives to form a semi-permeable membrane, and then drilling an orifice in the coating (e.g., with a laser). Kim, Cherng-ju, Controlled Release Dosage Form Design, 231-238 (Technomic Publishing, Lancaster, Pa.: 2000). The advantage of such dosage forms is that the delivery rate of the drug is not influenced by physiological or experimental conditions. Even a drug with a pH-dependent solubility can be delivered at a constant rate regardless of the pH of the delivery medium. But because these advantages are provided by a build-up of osmotic pressure within the dosage form after administration, conventional OROS® drug delivery systems cannot be used to effectively deliver drugs with low water solubility. Id. at 234. Because co-crystals of this invention can be far more soluble in water than the API itself, they are well suited for osmotic-based delivery to patients. This invention does, however, encompass the incorporation of conventional crystalline API (e.g. pure API without co-crystal former), and non-salt isomers and isomeric mixtures thereof, into OROS® dosage forms.

A specific dosage form of the invention comprises: a wall defining a cavity, the wall having an exit orifice formed or formable therein and at least a portion of the wall being semipermeable; an expandable layer located within the cavity remote from the exit orifice and in fluid communication with the semipermeable portion of the wall; a dry or substantially dry state drug layer located within the cavity adjacent to the exit orifice and in direct or indirect contacting relationship with the expandable layer; and a flow-promoting layer interposed between the inner surface of the wall and at least the external surface of the drug layer located within the cavity, wherein

the drug layer comprises a co-crystal, or a solvate, hydrate, dehydrate, anhydrous, or amorphous form thereof. See U.S. Pat. No. 6,368,626, the entirety of which is incorporated herein by reference.

Another specific dosage form of the invention comprises: a wall defining a cavity, the wall having an exit orifice formed or formable therein and at least a portion of the wall being semipermeable; an expandable layer located within the cavity remote from the exit orifice and in fluid communication with the semipermeable portion of the wall; a drug layer located within the cavity adjacent the exit orifice and in direct or indirect contacting relationship with the expandable layer; the drug layer comprising a liquid, active agent formulation absorbed in porous particles, the porous particles being adapted to resist compaction forces sufficient to form a compacted drug layer without significant exudation of the liquid, active agent formulation, the dosage form optionally having a placebo layer between the exit orifice and the drug layer, wherein the active agent formulation comprises a co-crystal, or a solvate, hydrate, dehydrate, anhydrous, or amorphous form thereof. See U.S. Pat. No. 6,342,249, the entirety of which is incorporated herein by reference.

The invention will now be described in further detail, by way of example, with reference to the accompanying drawings.

EXEMPLIFICATION

General Methods for the Preparation of Co-Crystals

a) High Throughput crystallization using the CrystalMax platform

CrystalMax™ comprises a sequence of automated, integrated high throughput robotic stations capable of rapid generation, identification and characterization of polymorphs, salts, and co-crystals of APIs and API candidates. Worksheet generation and combinatorial mixture design is carried out using proprietary design software InForm™. Typically, an API or an API candidate is dispensed from an organic solvent into tubes and dried under a stream of nitrogen. Salts and/or co-crystal formers may also be dispensed and dried in the same fashion. Water and organic solvents may be combinatorially dispensed into the tubes using a multi-channel dispenser. Each tube in a 96-tube array is then sealed within 15 seconds of combinatorial dispensing to avoid solvent evaporation. The mixtures are then

rendered supersaturated by heating to 70 degrees C for 2 hours followed by a 1 degree C/minute cooling ramp to 5 degrees C. Optical checks are then conducted to detect crystals and/or solid material. Once a solid has been identified in a tube, it is isolated through aspiration and drying. Raman spectra are then obtained on the solids and cluster classification of the spectral patterns is performed using proprietary software (QForm™).

b) Crystallization from solution

Co-crystals may be obtained by dissolving the separate components in a solvent and adding one to the other. The co-crystal may then precipitate or crystallize as the solvent mixture is evaporated slowly. The co-crystal may also be obtained by dissolving the two components in the same solvent or a mixture of solvents.

c) Crystallization from the melt

A co-crystal may be obtained by melting the two components together and allowing recrystallization to occur. In some cases, an anti-solvent may be added to facilitate crystallization.

d) Thermal microscopy

A co-crystal may be obtained by melting the higher melting component on a glass slide and allowing it to recrystallize. The second component is then melted and is also allowed to recrystallize. The co-crystal may form as a separated phase/band in between the eutectic bands of the two original components.

e) Mixing and/or grinding

A co-crystal may be obtained by mixing or grinding two components together in the solid state.

Analytical Methods

Procedure for DSC analysis

DSC analysis of the samples was performed using a Q1000 Differential Scanning Calorimeter (TA Instruments, New Castle, DE, U.S.A.), which uses Advantage for QW-Series, version 1.0.0.78, Thermal Advantage Release 2.0 (®2001 TA Instruments-Water LLC). In addition, the analysis software used was Universal Analysis 2000 for Windows 95/95/2000/NT, version 3.1E;Build 3.1.0.40 (®2001 TA Instruments-Water LLC).

For the DSC analysis, the purge gas used was dry nitrogen, the reference material was an empty aluminum pan that was crimped, and the sample purge was 50 mL/minute.

DSC analysis of the sample was performed by placing ≤ 2 mg of sample in an aluminum pan with a crimped pan closure. The starting temperature was typically 20 degrees C with a heating rate of 10 degrees C/minute, and the ending temperature was 300 degrees C. Unless otherwise indicated, all reported transitions are as stated +/- 1.0 degrees C.

Procedure for TGA analysis

TGA analysis of samples was performed using a Q500 Thermogravimetric Analyzer (TA Instruments, New Castle, DE, U.S.A.), which uses Advantage for QW-Series, version 1.0.0.78, Thermal Advantage Release 2.0 (©2001 TA Instruments-Water LLC). In addition, the analysis software used was Universal Analysis 2000 for Windows 95/95/2000/NT, version 3.1E;Build 3.1.0.40 (©2001 TA Instruments-Water LLC).

For all of the TGA experiments, the purge gas used was dry nitrogen, the balance purge was 40 mL/minute N_2, and the sample purge was 60 mL/minute N_2.

TGA of the sample was performed by placing ≤ 2 mg of sample in a platinum pan. The starting temperature was typically 20 degrees C with a heating rate of 10 degrees C/minute, and the ending temperature was 300 degrees C.

Procedure for PXRD analysis

A powder X-ray diffraction pattern for the samples was obtained using a D/Max Rapid, Contact (Rigaku/MSC, The Woodlands, TX, U.S.A.), which uses as its control software RINT Rapid Control software, Rigaku Rapid/XRD, version 1.0.0 (©1999 Rigaku Co.). In addition, the analysis software used were RINT Rapid display software, version 1.18 (Rigaku/MSC), and JADE XRD Pattern Processing, versions 5.0 and 6.0 ((©1995-2002, Materials Data, Inc.).

For the PXRD analysis, the acquisition parameters were as follows: source was Cu with a K line at 1.5406Å; x-y stage was manual; collimator size was 0.3 or 0.8 mm; capillary tube (Charles Supper Company, Natick, MA, U.S.A.) was 0.3 mm ID; reflection mode was used; the power to the X-ray tube was 46 kV; the current to the X-ray tube was 40 mA; the omega-axis was oscillating in a range of 0-5 degrees at a speed of 1 degree/minute; the phi-axis was spinning at an angle of 360 degrees at a speed of 2 degrees/second; 0.3 or 0.8 mm collimator; the collection time was 60 minutes; the temperature was room temperature; and the heater was not used. The sample was presented to the X-ray source in a boron rich glass capillary.

In addition, the analysis parameters were as follows: the integration 2-theta range was 2-40 or 60 degrees; the integration chi range was 0-360 degrees; the number of chi segments was 1; the step size used was 0.02; the integration utility was cylint; normalization was used; dark counts were 8; omega offset was 180; and chi and phi offsets were 0.

The relative intensity of peaks in a diffractogram is not necessarily a limitation of the PXRD pattern because peak intensity can vary from sample to sample, e.g., due to crystalline impurities. Further, the angles of each peak can vary by about +/- 0.1 degrees, preferably +/-0.05. The entire pattern or most of the pattern peaks may also shift by about +/- 0.1 degree due to differences in calibration, settings, and other variations from instrument to instrument and from operator to operator.

Procedure for Raman Acquisition, Filtering and Binning

Acquisition

The sample was either left in the glass vial in which it was processed or an aliquot of the sample was transferred to a glass slide. The glass vial or slide was positioned in the sample chamber. The measurement was made using an Almega™ Dispersive Raman (Almega™ Dispersive Raman, Thermo-Nicolet, 5225 Verona Road, Madison, WI 53711-4495) system fitted with a 785nm laser source. The sample was manually brought into focus using the microscope portion of the apparatus with a 10x power objective (unless otherwise noted), thus directing the laser onto the surface of the sample. The spectrum was acquired using the parameters outlined in Table A.

(Exposure times and number of exposures may vary; changes to parameters will be indicated for each acquisition.)

Filtering and Binning

Each spectrum in a set was filtered using a matched filter of feature size 25 to remove background signals, including glass contributions and sample fluorescence. This is particularly important as large background signal or fluorescence limit the ability to accurately pick and assign peak positions in the subsequent steps of the binning process. Filtered spectra were binned using the peak pick and bin algorithm with the parameters given in Table B. The sorted cluster diagrams for each sample set and the corresponding cluster assignments for each spectral file were used to identify groups of samples with similar spectra, which was used to identify samples for secondary analyses.

Table A. Raman Spectral acquisition parameters

Parameter	Setting Used
Exposure time (s)	2.0
Number of exposures	10
Laser source wavelength (nm)	785
Laser power (%)	100
Aperture shape	pin hole
Aperture size (um)	100
Spectral range	104-3428
Grating position	Single
Temperature at acquisition (degrees C)	24.0

Table B. Raman Filtering and Binning Parameters

Parameter	Setting Used
Filtering Parameters	
Filter type	Matched
Filter size	25
QC Parameters	
Peak Height Threshold	1000
Region for noise test (cm^{-1})	0-10000
RMS noise threshold	10000
Automatically eliminate failed spectra	Yes
Region of Interest	
Include (cm^{-1})	104-3428

Exclude region I (cm^{-1})	
Exclude region II (cm^{-1})	
Exclude region III (cm^{-1})	
Exclude region IV (cm^{-1})	
Peak Pick Parameters	
Peak Pick Sensitivity	Variable
Peak Pick Threshold	100
Peak Comparison Parameters	
Peak Window (cm^{-1})	2
Analysis Parameters	
Number of clusters	Variable

Procedure for Single Crystal X-Ray Diffraction

Single crystal x-ray data were collected on a Bruker SMART-APEX CCD diffractometer (M. J. Zawarotko, Department of Chemistry, University of South Florida). Lattice parameters were determined from least squares analysis. Reflection data was integrated using the program SAINT. The structure was solved by direct methods and refined by full matrix least squares using the program SHELXTL (Sheldrick, G. M. SHELXTL, Release 5.03; Siemans Analytical X-ray Instruments Inc.: Madison, WI).

The co-crystals of the present invention can be characterized, e.g., by the TGA or DSC data or by any one, any two, any three, any four, any five, any six, any seven, any eight, any nine, any ten, or any single integer number of PXRD 2-theta angle peaks or Raman shift peaks listed herein or disclosed in a figure, or by single crystal x-ray diffraction data.

Example 1

1:1 carbamazepine:saccharin co-crystals (Form I) were prepared. A 12-block experiment was designed with 12 solvents. 1152 crystallization experiments were carried out using the CMAX platform. The co-crystal was obtained from a mixture of isopropyl acetate and heptane. Detailed characterization of the co-crystal is listed in Table V. (See Figs. 1 and 2)

Example 2

1:1 carbamazepine:nicotinamide co-crystals (Form I) were prepared. A 12-block experiment was designed with 12 solvents. 1152 crystallization experiments were carried out using the CMAX platform. The co-crystal was obtained from samples containing toluene, acetone, or isopropyl acetate. Detailed characterization of the co-crystal is listed in Table V. (See Figs. 3 and 4)

Example 3

1:1 carbamazepine:trimesic acid co-crystals (Form I) were prepared. A 9-block experiment was designed with 10 solvents. 864 crystallization experiments with 8 co-crystal formers and 3 concentrations were carried out using the CMAX platform. The co-crystal was obtained from samples containing methanol. Detailed characterization of the co-crystal is listed in Table V. (See Fig. 5)

Example 4

1:1 celecoxib:nicotinamide co-crystals were prepared. Celecoxib (100 mg, 0.26 mmol) and nicotinamide (32.0 mg, 0.26 mmol) were each dissolved in acetone (2 mL). The two solutions were mixed and the resulting mixture was allowed to evaporate slowly overnight. The precipitated solid was collected and characterized. Detailed characterization of the co-crystal is listed in Table V.

Example 5

Co-crystals of topiramate and 18-crown-6 were prepared. An equimolar amount of topiramate and 18-crown-6 were dissolved in ether separately. The solution containing topiramate was then added to the solution containing 18-crown-6. A white solid precipitated after minor agitation and was collected and dried. Detailed characterization of the co-crystal is listed in Table V. (See Figs. 6 and 7)

Example 6

Co-crystals of olanzapine and nicotinamide (Form I and II) were prepared. A 9-block experiment was designed with 12 solvents. 864 crystallization experiments with 10 co-crystal formers and 3 concentrations were carried out using the CMAX platform. The co-crystal was obtained from tubes containing isopropyl acetate. PXRD and

DSC characterization of the co-crystal (Form I and II) is listed in Table V. (See Figs. 8, 9, and 30)

Example 7

Co-crystals of celecoxib and 18-crown-6 were prepared. A solution of celecoxib (157.8 mg, 0.4138 mmol) in Et_2O (10.0 mL) was added to 18-crown-6 (118.1 mg, 0.447 mmol). The opaque solid dissolves immediately and a white solid subsequently began to crystallize very rapidly. The solid was collected via filtration and was washed with additional Et_2O (5 mL). Detailed characterization of the co-crystal is listed in Table V. (See Figs. 10 and 11)

Example 8

Co-crystals of itraconazole and succinic acid were prepared. Approximately 51.1 mg of *cis*-itraconazole free base, 0.75 mL of THF, and a magnetic stir bar were charged into a screw cap vial, heated to reflux to dissolve, and then the vial was closed with the screw cap and placed on top of a hot plate maintained at a temperature between 60 and 75 degrees C. A solution of 77.7 mg of succinic acid in 1.58 mL of THF was prepared. 0.20 mL of the succinic acid solution was added to the cis-itraconazole solution and the solution remained clear. 0.75 mL of iso-propylacetate was added and the solution was seeded with <1 mg of the L-tartaric acid co-crystal salt from Example 10 below. The heat was turned off and the sample crystallized as it cooled to room temperature. The cooled sample was suction filtered. It was rinsed with 0.2-0.3 mL of THF. The filter cake was broken-up and allowed to air-dry for 1 hour prior to analysis. (See Figs. 12 and 13)

Example 9

Co-crystals of itraconazole and fumaric acid were prepared. Approximately 500 mg of *cis*-itraconazole free base was placed in a 50 mL screw top bottle along with 33.33 mL of tetrahydrofuran (THF). 3.0887 mL of fumaric acid stock solution (prepared in Example 1) was then added to the beaker (resulting in a 1.05:1 ratio of salt former to free base). The cap was screwed on to seal the bottle and the bottle was placed in a 70 degrees C oven (Model # 1400E, VWR Scientific) and heated for approximately 1 hour. Thereafter, the bottle was removed from the oven, the cap from the bottle was removed, and the sample was allowed to evaporate under flowing

air under ambient conditions. When all but about 5 mL of the solvent had evaporated, the remaining solvent was removed by decantation and the solid was isolated by filtering over a Whatman filter using suction. This solid was returned back into the 50 mL bottle with the remaining solid and the bottle was placed into the vacuum oven at approximately 25 mm Hg and the solid was allowed to dry for 4 days prior to analysis. (See Figs. 14 and 15)

Example 10

Co-crystals of itraconazole and tartaric acid were prepared. Approximately 100.4 mg of *cis*-itraconazole free base, 0.90 mL of THF, and a magnetic stir bar were charged into a screw cap vial, heated to reflux to dissolve, and then the vial was closed with the screw cap and placed in an oil bath maintained at 70 degrees C. A solution of 138.5 mg of L(+) tartaric acid in 1.15 mL of THF was prepared. 0.21 mL of the L(+)tartaric acid solution was added to the cis-itraconazole solution and the solution remained clear. 0.90 mL of iso-propylacetate was added and the solution was seeded with <1 mg of the salt from a preparation of DL-tartaric acid co-crystal. The sample was allowed to crystallize over about 5 minutes in the 70 degrees C oil bath before it was removed and allowed to cool to room temperature. The cooled sample was suction filtered. It was rinsed with 0.2-0.3 mL of THF. The filter cake was broken-up and allowed to air-dry for 4 hours prior to analysis. (See Figs. 16 and 17)

Example 11

Co-crystals of itraconazole and malic acid were prepared. To prepare the L-malic acid co-crystal salt of *cis*-itraconazole, 100.4 mg of *cis*-itraconazole free base, 0.50 mL of THF, and a magnetic stir bar were charged into a screw cap vial. A solution of 191.3 mg of L(-)malic acid in 5.0 mL of THF was prepared. 0.50 mL of the L-malic acid solution was added to the vial containing cis-itraconazole and the solution was heated with a heat gun to dissolve. The solution was allowed to cool and was then seeded with <1 mg of the salt from *cis*-itraconazole-L-tartaric acid co-crystal. The cooled crystals were filtered in a centrifuge filter tube. The filter cake was broken-up and allowed to air-dry prior to analysis. (See Figs. 18 and 19)

Example 12

Co-crystals of itraconazole HCl and tartaric acid were prepared. Approximately 212.7mg of L-tartaric acid and 118 microL of 37% HCl were dissolved in 25 mL of hot dioxane. This solution was added to 1.0 g of *cis*-itraconazole dissolved in 50 mL of hot dioxane with stirring. The mixture was heated until a clear solution formed and was then allowed to cool to room temperature. Upon cooling, 50 mL tert-butyl methyl ether was added and the crystals were harvested by vacuum filtration on a Buchner funnel with #4 Whatman filter paper. The crystals were washed 3 times with 5 mL aliquots of cold tert-butyl methyl ether and left to air dry. Approximately 573 mg of a crystalline form of cis-itraconazole HCl-tartaric acid (1:1:0.5) co-crystal were obtained. (See Figs. 20 and 21)

Example 13

Co-crystals of modafinil and malonic acid were prepared. Using a 250 mg/ml modafinil-acetic acid solution, malonic acid was dissolved on a hotplate (about 67 degrees C) at a 1:2 modafinil to malonic acid ratio. The mixture was dried under flowing nitrogen overnight. A powdery white solid was produced. After further drying for 1 day, acetic acid is removed (as determined by TGA) and the crystal structure, as determined by PXRD, remains the same. (See Fig. 22)

Example 14

Co-crystals of modafinil and benzamide were prepared. Modafinil (1 mg, 0.0037mmol) and benzamide (0.45 mg, 0.0037 mmol) were dissolved in 1,2-dichloroethane (400 microL). The solution was allowed to evaporate to dryness and the resulting solid was characterized using PXRD. PXRD data for the co-crystal is listed in Table V. (See Fig. 23)

Example 15

Co-crystals of modafinil and mandelic acid were prepared. Modafinil (1 mg, 0.0037mmol) and mandelic acid (0.55 mg, 0.0037 mmol) were dissolved in acetone (400 microL). The solution was allowed to evaporate to dryness and the resulting

solid was characterized using PXRD. PXRD data for the co-crystal is listed in Table V. (See Fig. 24)

Example 16

Co-crystals of modafinil and glycolic acid were prepared. Modafinil (1 mg, 0.0037mmol) and glycolic acid (0.30 mg, 0.0037 mmol) were dissolved in acetone (400 microL). The solution was allowed to evaporate to dryness and the resulting solid was characterized using PXRD. PXRD data for the co-crystal is listed in Table V. (See Fig. 25)

Example 17

Co-crystals of modafinil and fumaric acid were prepared. Modafinil (1 mg, 0.0037mmol) and fumaric acid (0.42 mg, 0.0037 mmol) were dissolved in 1,2-dichloroethane (400 microL). The solution was allowed to evaporate to dryness and the resulting solid was characterized using PXRD. PXRD data for the co-crystal is listed in Table V. (See Fig. 26)

Example 18

Co-crystals of modafinil and maleic acid were prepared. Using a 250 mg/ml modafinil-acetic acid solution, maleic acid was dissolved on a hotplate (about 67 degrees C) at a 2:1 modafinil to maleic ratio. The mixture was dried under flowing nitrogen overnight. A clear amorphous material remained. Solids began to grow after 2 days stored in a sealed vial at room temperature. (See Fig. 43)

Example 19

Co-crystals of olanzapine and nicotinamide (Form III) were prepared. Olanzapine (40 μL of 25 mg/mL stock solution in tetrahydrofuran) and nicotinamide (37.6 μL of 20 mg/mL stock solution in methanol) were added to a glass vial and dried under a flow of nitrogen. To the solid mixture was added isopropyl acetate (100 μL) and the vial was sealed with an aluminum cap. The suspension was then heated at 70 degrees C for two hours in order to dissolve all of the solid material. The solution was then cooled to 5 degrees C and maintained at that temperature for 24 hours. After 24 hours the vial was uncapped and the mixture was concentrated to 50 μL of total volume. The vial was then resealed with an aluminum cap and was maintained at 5 degrees C

for an additional 24 hours. Large, yellow plates were observed and were collected (Form III). The solid was characterized with single crystal x-ray diffraction and powder x-ray diffraction. PXRD characterization of the co-crystal is listed in Table V. (See Fig. 31 and 32A-D)

Single crystal x-ray analysis reveals that the olanzapine:nicotinamide (Form III) co-crystal is made up of a ternary system containing olanzapine, nicotinamide, water and isopropyl acetate in the unit cell. The co-crystal crystallizes in the monoclinic space group $P2_1/c$ and contains one olanzapine, one nicotinamide, 4 waters and one isopropyl acetate solvate in the asymmetric unit. The packing diagram is made up of a two-dimensional hydrogen-bonded network with the water molecules connecting the olanzapine and nicotinamide moieties. The packing diagram is also comprised of alternating olanzapine and nicotinamide layers connected through hydrogen bonding via the water and isopropyl acetate molecules, as shown in Figure 32B. The olanzapine layer propagates along the b axis at c/4 and 3c/4. The nicotinamide layer propagates along the b axis at c/2. The top of Figure 32C illustrates the nicotinamide superstructure. The nicotinamide molecules form dimers which hydrogen bond to chains of 4 water molecules. The water chains terminate with isopropyl acetate molecules on each side.

Crystal data: $C_{45}H_{64}N_{10}O_7S_2$, M = 921.18, monoclinic P21/c; a = 14.0961(12) Å, b = 12.5984(10) Å, c = 27.219(2) Å, $\alpha = 90°$, $\beta = 97.396(2)°$, $\gamma = 90°$, T = 100(2) K, $\mathbb{Z}$ = 4, $D_c = 1.276$ Mg/m^3, U = 4793.6(7) Å^3, $\lambda = 0.71073$ Å; 24952 reflections measured, 8457 unique ($R_{int} = 0.0882$). Final residuals were $R_1 = 0.0676$, $wR_2 = 0.1461$ for $I>2\sigma(I)$, and $R_1 = 0.1187$, $wR_2 = 0.1687$ for all 8457 data.

Example 20

Co-crystals of 5-fluorouracil and urea were prepared. To 5-fluorouracil (1g, 7.69 mmol) and urea (0.46g, 7.69 mmol) was added methanol (100 mL). The solution was heated at 65 degrees C and sonicated until all the material dissolved. The solution was then cooled to 5 degrees C and maintained at that temperature overnight. After about 3 days a white precipitate was observed and collected. The solid was characterized by DSC, PXRD, Raman spectroscopy, and TGA. Characterization data are listed in Table V. (See Figs. 33- 36)

Example 21

Co-crystals of hydrochlorothiazide and nicotinic acid were prepared. Hydrochlorothiazide (12.2 mg, 0.041 mmol) and nicotinic acid (5 mg, 0.041 mmol) were dissolved in methanol (1 mL). The solution was then cooled to 5 degrees C and maintained at that temperature for 12 hours. A white solid precipitated and was collected and characterized using PXRD. (See Fig. 37)

Example 22

Co-crystals of hydrochlorothiazide and 18-crown-6 were prepared. Hydrochlorothiazide (100 mg, 0.33 mmol) was dissolved in diethyl ether (15 mL) and was added to a solution of 18-crown-6 (87.2 mg, 0.33 mmol) in diethyl ether (15 mL). A white precipitate immediately began to form and was collected and characterized as the hydrochlorothiazide:18-crown-6 co-crystal using PXRD. (See Fig. 38)

Example 23

Co-crystals of hydrochlorothiazide and piperazine were prepared. Hydrochlorothiazide (17.3 mg, 0.058 mmol) and piperazine (5 mg, 0.058 mmol) were dissolved in a 1:1 mixture of ethyl acetate and acetonitirle (1 mL). The solution was then cooled to 5 degrees C and maintained at that temperature for 12 hours. A white solid precipitated and was collected and characterized using PXRD. (See Fig. 39)

Example 24

Acetaminophen:4,4'-bipyridine:water (1:1:1 stoichiometry)

50 mg (0.3307 mmol) acetaminophen and 52 mg (0.3329 mmol) 4,4'-bipyridine were dissolved in hot water and allowed to stand. Slow evaporation yielded colorless needles of a 1:1:1 acetaminophen/4,4'-bipyridine/water co-crystal, as shown in Figure 44A-B.

Crystal data: (Bruker SMART-APEX CCD Diffractometer). $C_{36}H_{44}N_2O_4$, M=339.84, triclinic, space group *P*$\bar{1}$; a = 7.0534(8), b = 9.5955(12), c = 19.3649(2) Å, α = 86.326(2), β = 80.291(2), γ = 88.880(2)°, *U* = 1308.1(3) Å^3, T = 200(2) K, Z = 2, μ(Mo-Kα) = 0.090 mm^{-1}, D_c = 1.294 Mg/m^3, λ = 0.71073 Å, F(000) = 537, $2\theta_{max}$ = 25.02°; 6289 reflections measured, 4481 unique (R_{int} = 0.0261). Final

residuals for 344 parameters were $R_1 = 0.0751$, $wR_2 = 0.2082$ for $I>2\sigma(I)$, and $R_1 = 0.1119$, $wR_2 = 0.2377$ for all 4481data.

Crystal packing: The co-crystals contain bilayered sheets in which water molecules act as a hydrogen bonded bridge between the network bipyridine moieties and the acetaminophen. Bipyridine guests are sustained by π-π stacking interactions between two network bipyridines. The layers stack via π-π interactions between the phenyl groups of the acetaminophen moieties.

Differential Scanning Calorimetry: (TA Instruments 2920 DSC), 57.77 degrees C (endotherm); m.p. = 58-60 degrees C (MEL-TEMP); (acetaminophen m.p. = 169 degrees C, 4,4'-bipyridine m.p. = 111-114 degrees C).

Example 25

Phenytoin:Pyridone (1:1 stoichiometry)

28 mg (0.1109 mmol) phenytoin and 11 mg (0.1156 mmol) 4-hydroxypyridone were dissolved in 2 mL acetone and 1 mL ethanol with heating and stirring. Slow evaporation yielded colorless needles of a 1:1 phenytoin/pyridone co-crystal, as shown in Figure 45A-B.

Crystal data: (Bruker SMART-APEX CCD Diffractometer), $C_{20}H_{17}N_3O_3$, M = 347.37, monoclinic $P2_1/c$; a = 16.6583(19), b = 8.8478(10), c = 11.9546(14) Å, β = 96.618(2)°, U = 1750.2(3) Å^3, T = 200(2) K, Z = 4, μ(Mo-Kα) = 0.091 mm^{-1}, D_c = 1.318 Mg/m^3, λ = 0.71073 Å, F(000) = 728, $2\theta_{max}$ = 56.60°; 10605 reflections measured, 4154 unique (R_{int} = 0.0313). Final residuals for 247 parameters were $R_1 = 0.0560$, $wR_2 = 0.1356$ for $I>2\sigma(I)$, and $R_1 = 0.0816$, $wR_2 = 0.1559$ for all 4154 data.

Crystal packing: The co-crystal is sustained by hydrogen bonding of adjacent phentoin molecules between the carbonyl and the amine closest to the tetrahedral carbon, and by hydrogen bonding between pyridone carbonyl functionalities and the amine not involved in phenytoin-phenytoin interactions. The pyridone carbonyl also hydrogen bonds with adjacent pyridone molecules forming a one-dimensional network.

Infrared Spectroscopy: (Nicolet Avatar 320 FTIR), characteristic peaks for the co-crystal were identified as: 2° amine found at 3311cm^{-1}, carbonyl (ketone) found at 1711cm^{-1}, olephin peak found at 1390cm^{-1}.

Differential Scanning Calorimetry: (TA Instruments 2920 DSC), 233.39 degrees C (endotherm) and 271.33 degrees C (endotherm); m.p. = 231-233 degrees C (MEL-TEMP); (phenytoin m.p. = 295 degrees C, pyridone m.p. = 148 degrees C).

Thermogravimetric Analysis: (TA Instruments 2950 Hi-Resolution TGA), a 29.09% weight loss starting at 192.80 degrees C, 48.72% weight loss starting at 238.27 degrees C, and 18.38% loss starting at 260.17 degrees C followed by complete decomposition.

Powder x-ray diffraction: (Rigaku Miniflex Diffractometer using Cu Kα (λ = 1.540562), 30kV, 15mA). The powder data were collected over an angular range of 3° to 40° 2θ in continuous scan mode using a step size of 0.02° 2θ and a scan speed of 2.0°/minute. PXRD: Showed analogous peaks to the simulated PXRD derived from the single crystal data. In all cases of recrystallization and solid state reaction, experimental (calculated): 5.2 (5.3); 11.1 (11.3); 15.1 (15.2); 16.2 (16.4); 16.7 (17.0); 17.8 (17.9); 19.4 (19.4); 19.8 (19.7); 20.3 (20.1); 21.2 (21.4); 23.3 (23.7); 26.1 (26.4); 26.4 (26.6); 27.3 (27.6); 29.5 (29.9).

Example 26

Aspirin (acetylsalicylic acid):4,4'-bipyridine (2:1 stoichiometry)

50 mg (0.2775 mmol) aspirin and 22 mg (0.1388 mmol) 4,4'-bipyridine were dissolved in 4 mL hexane. 8 mL ether was added to the solution and allowed to stand for one hour, yielding colorless needles of a 2:1 aspirin/4,4'-bipyridine co-crystal, as shown in Figure 46A-D. Alternatively, aspirin/4,4'-bipyridine (2:1 stoichiometry) can be made by grinding the solid ingredients in a pestle and mortar.

Crystal data: (Bruker SMART-APEX CCD Diffractometer), $C_{28}H_{24}N_2O_8$, M = 516.49, orthorhombic *Pbcn*; a = 28.831(3), b = 11.3861(12), c = 8.4144(9) Å, U = 2762.2(5) Å^3, T = 173(2) K, Z = 4, μ(Mo-Kα) = 0.092 mm^{-1}, D_c = 1.242 Mg/m^3, λ = 0.71073 Å, F(000) = 1080, $2\theta_{max}$ = 25.02°; 12431 reflections measured, 2433 unique (R_{int} = 0.0419). Final residuals for 202 parameters were R_1 = 0.0419, wR_2 = 0.1358 for I>2σ(I), and R_1 = 0.0541, wR_2 = 0.1482 for all 2433 data.

Crystal packing: The co-crystal contains the carboxylic acid-pyridine heterodimer that crystallizes in the *Pbcn* space group. The structure is an inclusion compound containing disordered solvent in the channels. In addition to the dominant hydrogen bonding interaction of the heterodimer, π-π stacking of the bipyridine and

phenyl groups of the aspirin and hydrophobic interactions contribute to the overall packing interactions.

Infrared Spectroscopy: (Nicolet Avatar 320 FTIR), characteristic (-COOH) peak at 1679 cm^{-1} was shifted up and less intense at 1694cm^{-1}, where as the lactone peak is shifted down slightly from 1750cm^{-1} to 1744cm^{-1}.

Differential Scanning Calorimetry: (TA Instruments 2920 DSC), 95.14 degrees C (endotherm); m.p. = 91-96 degrees C (MEL-TEMP); (aspirin m.p. = 1345 degrees C, 4,4'-bipyridine m.p. = 111-114 degrees C).

Thermogravimetric Analysis: (TA Instruments 2950 Hi-Resolution TGA), weight loss of 9% starting at 22.62 degrees C, 49.06% weight loss starting at 102.97 degrees C followed by complete decomposition starting at 209.37 degrees C.

Example 27

Ibuprofen:4,4'-Bipyridine (2:1 stoichiometry)

50 mg (0.242 mmol) racemic ibuprofen and 18mg (0.0960 mmol) 4,4'-bipyridine were dissolved in 5 mL acetone. Slow evaporation of the solvent yielded colorless needles of a 2:1 ibuprofen/4,4'-bipyridine co-crystal, as shown in Figure 47A-D.

Crystal data: (Bruker SMART-APEX CCD Diffractometer), $C_{36}H_{44}N_2O_4$, M = 568.73, triclinic, space group *P-1*; a = 5.759(3), b = 11.683(6), c = 24.705(11) Å, α = 93.674(11), β = 90.880(10), γ = 104.045(7)°, *U* = 1608.3(13) $Å^3$, T= 200(2) K, Z = 2, μ(Mo-Kα) = 0.076 mm^{-1}, D_c = 1.174 Mg/m^3, λ = 0.71073 Å, F(000) = 612, $2\theta_{max}$ = 23.29°; 5208 reflections measured, 3362 unique (R_{int} = 0.0826). Final residuals for 399 parameters were R_1 = 0.0964, wR_2 = 0.2510 for I>2σ(I), and R_1 = 0.1775, wR_2 = 0.2987 for all 3362 data.

Crystal packing: The co-crystal contains ibuprofen/bipyridine heterodimers, sustained by two hydrogen bonded carboxylic acidpyridine supramolecular synthons, arranged in a herringbone motif that packs in the space group *P-1*. The heterodimer is an extended version of the homodimer and packs to form a two-dimensional network sustained by π-π stacking of the bipyridine and phenyl groups of the ibuprofen and hydrophobic interactions from the ibuprofen tails.

Infrared Spectroscopy: (Nicolet Avatar 320 FTIR). Analysis observed stretching of aromatic C-H at 2899 cm^{-1}; N--H bending and scissoring at 1886 cm_{-1};

C=O stretching at 1679 cm^{-1}; C-H out-of-plane bending for both 4,4'-bipyridine and ibuprofen at 808 cm^{-1} and 628 cm^{-1}.

Differential Scanning Calorimetry: (TA Instruments 2920 DSC), 64.85 degrees C (endotherm) and 118.79 degrees C (endotherm); m.p. = 113-120 degrees C (MEL-TEMP); (ibuprofen m.p. = 75-77 degrees C, 4,4'-bipyridine m.p. = 111-114 degrees C).

Thermogravimetric Analysis: (TA Instruments 2950 Hi-Resolution TGA), 13.28% weight loss between room temperature and 100.02 degrees C immediately followed by complete decomposition.

Powder x-ray diffraction: (Rigaku Miniflex Diffractometer using Cu Kα (λ = 1.540562), 30kV, 15mA). The powder data were collected over an angular range of 3° to 40° 2θ in continuous scan mode using a step size of 0.02° 2θ and a scan speed of 2.0°/minute. PXRD derived from the single crystal data, experimental (calculated): 3.4 (3.6); 6.9 (7.2); 10.4 (10.8); 17.3 (17.5); 19.1 (19.7).

Example 28

Flurbiprofen:4,4'-bipyridine (2:1 stoichiometry)

50 mg (0.2046 mmol) flurbiprofen and 15 mg (0.0960 mmol) 4,4'-bipyridine were dissolved in 3 mL acetone. Slow evaporation of the solvent yielded colorless needles of a 2:1 flurbiprofen/4,4'-bipyridine co-crystal, as shown in Figure 48A-D.

Crystal data: (Bruker SMART-APEX CCD Diffractometer), $C_{40}H_{34}F_2N_2O_4$, M = 644.69, monoclinic *P2₁/n*; a = 5.860(4), b = 47.49(3), c = 5.928(4) Å, β = 107.382 (8)°, U = 1574.3(19) $Å^3$, T = 200(2) K, Z = 2, μ(Mo-Kα) = 0.096 mm^{-1}, D_c = 1.360 Mg/m^3, λ = 0.71073 Å, F(000) = 676, $2\theta_{max}$ = 21.69°; 4246 reflections measured, 1634 unique (R_{int} = 0.0677). Final residuals for 226 parameters were R_1 = 0.0908, wR_2 = 0.2065 for I>2σ(I), and R_1 = 0.1084, wR_2 = 0.2209 for all 1634 data.

Crystal packing: The co-crystal contains flurbiprofen/bipyridine heterodimers, sustained by two hydrogen bonded carboxylic acidpyridine supramolecular synthon, arranged in a herringbone motif that packs in the space group *P2₁/n*. The heterodimer is an extended version of the homodimer and packs to form a two-dimensional network sustained by π-π stacking and hydrophobic interactions of the bipyridine and phenyl groups of the flurbiprofen.

Infrared Spectroscopy: (Nicolet Avatar 320 FTIR), aromatic C-H stretching at 3057 cm^{-1} and 2981 cm^{-1}; N–H bending and scissoring at 1886 cm^{-1}; C=O stretching at 1690 cm^{-1}; C=C and C=N ring stretching at 1418 cm^{-1}.

Differential Scanning Calorimetry: (TA Instruments 2920 DSC), 162.47 degrees C (endotherm); m.p. = 155-160 degrees C (MEL-TEMP); (flurbiprofen m.p. = 110-111 degrees C, 4,4'-bipyridine m.p. = 111-114 degrees C).

Thermogravimetric Analysis: (TA Instruments 2950 Hi-Resolution TGA), 30.93% weight loss starting at 31.13 degrees C and a 46.26% weight loss starting at 168.74 degrees C followed by complete decomposition.

Powder x-ray diffraction: (Rigaku Miniflex Diffractometer using Cu Kα (λ = 1.540562), 30kV, 15mA), the powder data were collected over an angular range of 3° to 40° 2θ in continuous scan mode using a step size of 0.02° 2θ and a scan speed of 2.0°/minute. PXRD derived from the single crystal data: experimental (calculated): 16.8 (16.8); 17.1 (17.5); 18.1 (18.4); 19.0 (19.0); 20.0 (20.4); 21.3 (21.7); 22.7 (23.0); 25.0 (25.6); 26.0 (26.1); 26.0 (26.6); 26.1 (27.5); 28.2 (28.7); 29.1 (29.7).

Example 29

Flurbiprofen:trans-1,2-bis (4-pyridyl) ethylene (2:1 stoichiometry)

25 mg (0.1023 mmol) flurbiprofen and 10 mg (0.0548 mmol) trans-1, 2-bis (4-pyridyl) ethylene were dissolved in 3 mL acetone. Slow evaporation of the solvent yielded colorless needles of a 2:1 flurbiprofen/1,2-bis (4-pyridyl) ethylene co-crystal, as shown in Figure 49A-B.

Crystal data: (Bruker SMART-APEX CCD Diffractometer), $C_{42}H_{36}F_2N_2O_4$, M = 670.73, monoclinic $P2_1/n$; a = 5.8697(9), b = 47.357(7), c = 6.3587(10) Å, β = 109.492(3)°, U = 1666.2(4) $Å^3$, T = 200(2) K, Z = 2, μ(Mo-Kα) = 0.093 mm^{-1}, D_c = 1.337 Mg/m^3, λ = 0.71073 Å, F(000) = 704, $2\theta_{max}$ = 21.69°, 6977 reflections measured, 2383 unique (R_{int} = 0.0383). Final residuals for 238 parameters were R_1 = 0.0686, wR_2 = 0.1395 for I>2σ(I), and R_1 = 0.1403, wR_2 = 0.1709 for all 2383 data.

Crystal packing: The co-crystal contains flurbiprofen/1,2-bis (4-pyridyl) ethylene heterodimers, sustained by two hydrogen bonded carboxylic acid-pyridine supramolecular synthons, arranged in a herringbone motif that packs in the space group $P2_1/n$. The heterodimer from 1,2-bis (4-pyridyl) ethylene further extends the homodimer relative to example 28 and packs to form a two-dimensional network

sustained by π-π stacking and hydrophobic interactions of the bipyridine and phenyl groups of the flurbiprofen.

Infrared Spectroscopy: (Nicolet Avatar 320 FTIR), aromatic C-H stretching at 2927 cm^{-1} and 2850 cm^{-1}; N--H bending and scissoring at 1875 cm^{-1}; C=O stretching at 1707 cm^{-1}; C=C and C=N ring stretching at 1483 cm^{-1}.

Differential Scanning Calorimetry: (TA Instruments 2920 DSC), 100.01 degrees C, 125.59 degrees C and 163.54 degrees C (endotherms); m.p. = 153-158 degrees C (MEL-TEMP); (flurbiprofen m.p. = 110-111 degrees C, trans-1, 2-bis (4-pyridyl) ethylene m.p. = 150-153 degrees C).

Thermogravimetric Analysis: (TA Instruments 2950 Hi-Resolution TGA), 91.79% weight loss starting at 133.18 degrees C followed by complete decomposition.

Powder x-ray diffraction: (Rigaku Miniflex Diffractometer using Cu Kα (λ = 1.540562), 30kV, 15mA), the powder data were collected over an angular range of 3° to 40° 2θ in continuous scan mode using a step size of 0.02° 2θ and a scan speed of 2.0°/minute. PXRD derived from the single crystal data, experimental (calculated): 3.6 (3.7); 17.3 (17.7); 18.1 (18.6); 18.4 (18.6); 19.1 (19.3); 22.3 (22.5); 23.8 (23.9); 25.9 (26.4); 28.1 (28.5).

Example 30

Carbamazepine:*p*-Phthalaldehyde (1:1 stoichiometry)

25 mg (0.1058 mmol) carbamazepine and 7 mg (0.0521 mmol) *p*-phthalaldehyde were dissolved in approximately 3 mL methanol. Slow evaporation of the solvent yielded colorless needles of a 1:1 carbamazepine/*p*-phthalaldehyde co-crystal, as shown in Figure 50A-B.

Crystal data: (Bruker SMART-APEX CCD Diffractometer), $C_{38}H_{30}N_4O_4$, M = 606.66, monoclinic *C2/c*; a = 29.191(16), b = 4.962(3), c = 20.316(11) Å, β = 92.105(8)°, *U* = 2941(3) $Å^3$, T= 200(2) K, Z = 4, μ(Mo-Kα) = 0.090 mm^{-1}, D_c = 1.370 Mg/m^3, λ = 0.71073 Å, F(000) = 1272, $2\theta_{max}$ = 43.66°, 3831 reflections measured, 1559 unique (R_{int} = 0.0510). Final residuals for 268 parameters were R_1 = 0.0332, wR_2 = 0.0801 for I>2σ(I), and R_1 = 0.0403, wR_2 = 0.0831 for all 1559 data.

Crystal packing: The co-crystals contain hydrogen bonded carboxamide homodimers that crystallize in the space group *C2/c*. The 1° amines of the

homodimer are bifurcated to the carbonyl of the *p*-phthalaldehyde forming a chain with an adjacent homodimer. The chains pack in a crinkled tape motif sustained by π-π interactions between phenyl rings of the CBZ.

Infrared Spectroscopy: (Nicolet Avatar 320 FTIR). The 1° amine unsymmetrical and symmetrical stretching was shifted down to 3418 cm^{-1}; aliphatic aldehyde and 1° amide C=O stretching was shifted up to 1690 cm^{-1}; N-H in-plane bending at 1669 cm^{-1}; C-H aldehyde stretching at 2861 cm^{-1} and H-C=O bending at 1391 cm^{-1}.

Differential Scanning Calorimetry: (TA Instruments 2920 DSC), 128.46 degrees C (endotherm), m.p. = 121-124 degrees C (MEL-TEMP), (carbamazepine m.p. = 190.2 degrees C, *p*-phthalaldehyde m.p. = 116 degrees C).

Thermogravimetric Analysis: (TA Instruments 2950 Hi-Resolution TGA), 17.66% weight loss starting at 30.33 degrees C then a 17.57% weight loss starting at 100.14 degrees C followed by complete decomposition.

Powder x-ray diffraction: (Rigaku Miniflex Diffractometer using Cu Kα (λ = 1.540562), 30kV, 15mA). The powder data were collected over an angular range of 3° to 40° 2θ in continuous scan mode using a step size of 0.02° 2θ and a scan speed of 2.0°/minute. PXRD derived from the single crystal data, experimental (calculated): 8.5 (8.7); 10.6 (10.8); 11.9 (12.1); 14.4 (14.7) 15.1 (15.2); 18.0 (18.1); 18.5 (18.2); 19.8 (18.7); 23.7 (24.0); 24.2 (24.2); 26.4 (26.7); 27.6 (27.9); 27.8 (28.2); 28.7 (29.1); 29.3 (29.6); 29.4 (29.8).

Example 31

Carbamazepine:nicotinamide (Form II) (1:1 stoichiometry)

25 mg (0.1058 mmol) carbamazepine and 12 mg (0.0982 mmol) nicotinamide were dissolved in 4 mL of DMSO, methanol or ethanol. Slow evaporation of the solvent yielded colorless needles of a 1:1 carbamazepine/nicotinamide co-crystal, as shown in Figure 51.

Using a separate method, 25 mg (0.1058 mmol) carbamazepine and 12 mg (0.0982mmol) nicotinamide were ground together with mortar and pestle. The solid was determined to be 1:1 carbamazepine/nicotinamide microcrystals (PXRD).

Crystal data: (Bruker SMART-APEX CCD Diffractometer), $C_{21}H_{18}N_4O_2$, M = 358.39, monoclinic $P2_1/n$; a = 5.0961(8), b = 17.595(3), c = 19.647(3) Å, β = 90.917(3)°, U = 1761.5(5) $Å^3$, T = 200(2) K, Z = 4, μ(Mo-Kα) = 0.090 mm^{-1},

D_c = 1.351 Mg/m^3, λ = 0.71073 Å, F(000) = 752, $2\theta_{max}$ = 56.60°, 10919 reflections measured, 4041 unique (R_{int} = 0.0514). Final residuals for 248 parameters were R_1 = 0.0732, wR_2 = 0.1268 for I>2σ(I), and R_1 = 0.1161, wR_2 = 0.1430 for all 4041 data.

Crystal packing: The co-crystals contain hydrogen bonded carboxamide homodimers. The 1° amines are bifurcated to the carbonyl of the nicotinamide on each side of the dimer. The 1° amines of each nicotinamide are hydrogen bonded to the carbonyl of the adjoining dimer. The dimers form chains with π-π interactions from the phenyl groups of the CBZ.

Infrared Spectroscopy: (Nicolet Avatar 320 FTIR), unsymmetrical and symmetrical stretching shifts down to 3443 cm^{-1} and 3388 cm^{-1} accounting for 1° amines; 1° amide C=O stretching at 1690 cm^{-1}; N-H in-plane bending at 1614 cm^{-1}; C=C stretching shifted down to 1579 cm^{-1}; aromatic H's from 800 cm^{-1} to 500 cm^{-1} are present.

Differential Scanning Calorimetry: (TA Instruments 2920 DSC), 74.49 degrees C (endotherm) and 159.05 degrees C (endotherm), m.p. = 153-158 degrees C (MEL-TEMP), (carbamazepine m.p. = 190.2 degrees C, nicotinamide m.p. = 150-160 degrees C).

Thermogravimetric Analysis: (TA Instruments 2950 Hi-Resolution TGA), 57.94% weight loss starting at 205.43 degrees C followed by complete decomposition.

Powder x-ray diffraction: (Rigaku Miniflex Diffractometer using Cu Kα (λ = 1.540562), 30kV, 15mA). The powder data were collected over an angular range of 3° to 40° 2θ in continuous scan mode using a step size of 0.02° 2θ and a scan speed of 2.0°/minute. PXRD: Showed analogous peaks to the simulated PXRD derived from the single crystal data. PXRD analysis experimental (calculated): 6.5 (6.7); 8.8 (9.0); 10.1 (10.3); 13.2 (13.5); 15.6 (15.8); 17.7 (17.9); 17.8 (18.1); 18.3 (18.6); 19.8 (20.1); 20.4 (20.7); 21.6 (22.); 22.6 (22.8); 22.9 (23.2); 26.4 (26.7); 26.7 (27.0); 28.0 (28.4).

Example 32

Carbamazepine:saccharin (Form II) (1:1 stoichiometry)

25 mg (0.1058mmol) carbamazepine and 19 mg (0.1037 mmol) saccharin were dissolved in approximately 4 mL ethanol. Slow evaporation of the solvent

yielded colorless needles of a 1:1 carbamazepine/saccharin cocrystal, as shown in Figure 52. Solubility measurements indicate that this multiple-component crystal of carbamazepine has improved solubility over previously known forms of carbamazepine (*e.g.*, increased molar solubility and longer solubility in aqueous solutions).

Crystal data: (Bruker SMART-APEX CCD Diffractometer), $C_{22}H_{17}N_3O_4S_1$, M = 419.45, triclinic *P-1*; a = 7.5140(11), b = 10.4538(15), c = 12.6826(18) Å, α = 83.642(2)°, β = 85.697(2) °, γ = 75.411(2) °, *U* = 957.0(2) Å^3, T = 200(2) K, Z = 2, μ(Mo-Kα) = 0.206 mm^{-1}, D_c = 1.456 Mg/m^3, λ = 0.71073 Å, F(000) = 436, $2\theta_{max}$ = 56.20°; 8426 reflections measured, 4372 unique (R_{int} = 0.0305). Final residuals for 283 parameters were R_1 = 0.0458, wR_2 = 0.1142 for I>2σ(I), and R_1 = 0.0562, wR_2 = 0.1204 for all 4372 data.

Crystal packing: The co-crystals contain hydrogen bonded carboxamide homodimers. The 2° amines of the saccharin are hydrogen bonded to the carbonyl of the CBZ on each side forming a tetramer. The crystal has a space group of *P-1* with π-π interactions between the phenyl groups of the CBZ and the saccharin phenyl groups.

Infrared Spectroscopy: (Nicolet Avatar 320 FTIR), unsymmetrical and symmetrical stretching shifts up to 3495 cm^{-1} accounting for 1° amines; C=O aliphatic stretching was shifted up to 1726 cm^{-1}; N-H in-plane bending at 1649 cm^{-1}; C=C stretching shifted down to 1561 cm^{-1}; (O=S=O) sulfonyl peak at 1330 cm^{-1} C-N aliphatic stretching 1175 cm^{-1}.

Differential Scanning Calorimetry: (TA Instruments 2920 DSC), 75.31 degrees C (endotherm) and 177.32 degrees C (endotherm), m.p. = 148-155 degrees C (MEL-TEMP); (carbamazepine m.p. = 190.2 degrees C, saccharin m.p. = 228.8 degrees C).

Thermogravimetric Analysis: (TA Instruments 2950 Hi-Resolution TGA), 3.342% weight loss starting at 67.03 degrees C and a 55.09% weight loss starting at 118.71 degrees C followed by complete decomposition.

Powder x-ray diffraction: (Rigaku Miniflex Diffractometer using Cu Kα (λ = 1.540562), 30kV, 15mA). The powder data were collected over an angular range of 3° to 40° 2θ in continuous scan mode using a step size of 0.02° 2θ and a scan speed of 2.0°/minute. PXRD derived from the single crystal data, experimental (calculated):

6.9 (7.0); 12.2 (12.2); 13.6 (13.8); 14.0 (14.1); 14.1 (14.4); 15.3 (15.6); 15.9 (15.9); 18.1 (18.2); 18.7 (18.8); 20.2 (20.3); 21.3 (21.5); 23.7 (23.9); 26.3 (26.4); 28.3 (28.3).

Example 33

Carbamazepine:2,6-pyridinedicarboxylic acid (2:3 stoichiometry)

36 mg (0.1524 mmol) carbamazepine and 26 mg (0.1556 mmol) 2,6-pyridinedicarboxylic acid were dissolved in approximately 2 mL ethanol. Slow evaporation of the solvent yielded clear needles of a 1:1 carbamazepine/2,6-pyridinedicarboxylic acid co-crystal, as shown in Figure 54A-B.

Crystal data: (Bruker SMART-APEX CCD Diffractometer). $C_{22}H_{17}N_3O_5$, M=403.39, orthorhombic P2(1)2(1)2(1); a=7.2122, b=14.6491, c=17.5864 Å,α=90°, β=90°, γ=90°, V=1858.0(2) $Å^3$, T=100 K, Z=4, μ(MO-Kα)=0.104 mm^{-1}, D_c=1.442 Mg/m^3, λ=0.71073Å , F(000)840, $2\theta_{max}$=28.3. 16641 reflections measured, 4466 unique (R_{int}=0.093). Final residuals for 271 parameters were R_1=0.0425 and wR_2=0.0944 for I>2σ(I).

Crystal packing: Each hydrogen on the CBZ 1° amine is hydrogen bonded to a carbonyl group of a different 2,6-pyridinedicarboxylic acid moiety. The carbonyl of the CBZ carboxamide is hydrogen bonded to two hydroxide groups of one 2,6-pyridinedicarboxylic acid moitey.

Infrared Spectroscopy: (Nicolet Avatar 320 FTIR). 3439 cm^{-1}, (N-H stretch, 1° amine, CBZ); 1734 cm^{-1}, (C=O); 1649 cm^{-1}, (C=C).

Melting Point: 214-216 degrees C (MEL-TEMP). (carbamazepine m.p. = 191-192 degrees C, 2,6-pyridinedicarboxylic acid m.p. = 248-250 degrees C).

Thermogravimetric Analysis: (TA Instruments 2950 Hi-Resolution TGA). 69% weight loss starting at 215 degrees C and a 17% weight loss starting at 392 degrees C followed by complete decomposition.

Example 34

Carbamazepine:5-nitroisophthalic acid (1:1 stoichiometry)

40 mg (0.1693 mmol) carbamazepine and 30 mg (0.1421 mmol) 5-nitroisophthalic acid were dissolved in approximately 3 mL methanol or ethanol. Slow evaporation of the solvent yielded yellow needles of a 1:1 carbamazepine/5-nitroisophthalic acid co-crystal, as shown in Figure 55A-B.

Crystal data: (Bruker SMART-APEX CCD Diffractometer). $C_{47}H_{40}N_6O_{16}$, M=944.85, monoclinic C2/c; a=34.355(8), b=5.3795(13), c=23.654(6) Å,α=90°, β=93.952(6)°, γ=90°, V=4361.2(18)Å^3, T=200(2) K, Z=4, μ(MO-Kα)=0.110 mm^{-1}, D_c=1.439 Mg/m^3, λ=0.71073Å, F(000)1968, $2\theta_{max}$=26.43°. 11581 reflections measured, 4459 unique (R_{int}=0.0611). Final residuals for 311 parameters were R_1=0.0725, wR_2=0.1801 for I>2σ(I), and R_1=0.1441, wR_2=0.1204 for all 4459 data.

Crystal packing: The co-crystals are sustained by hydrogen bonded carboxylic acid homodimers between the two 5-nitroisophthalic acid moieties and hydrogen bonded carboxy-amide heterodimers between the carbamazepine and 5-nitroisophthalic acid moiety. There is solvent hydrogen bonded to an additional N-H donor from the carbamazepine moiety.

Infrared Spectroscopy: (Nicolet Avatar 320 FTIR). 3470 cm^{-1}, (N-H stretch, 1° amine, CBZ); 3178 cm^{-1}, (C-H stretch, alkene); 1688 cm^{-1}, (C=O); 1602 cm^{-1}, (C=C).

Differential Scanning Calorimetry: (TA Instruments 2920 DSC). 190.51 degrees C (endotherm). m.p. = NA (decomposes at 197-200 degrees C) (MEL-TEMP). (carbamazepine m.p. = 191-192 degrees C, 5-nitroisophthalic acid m.p. = 260-261 degrees C).

Thermogravimetric Analysis: (TA Instruments 2950 Hi-Resolution TGA). 32.02% weight loss starting at 202 degrees C, a 12.12% weight loss starting at 224 degrees C and a 17.94% weight loss starting at 285 degrees C followed by complete decomposition.

Powder x-ray diffraction: (Rigaku Miniflex Diffractometer using CuKα (λ=1.540562), 30kV, 15mA). The powder data were collected over an angular range of 3 to 40 2 in continuous scan mode using a step size of 0.02 2 and a scan speed of 2.0 /min. PXRD: Showed analogous peaks to the simulated PXRD derived from the single crystal data. PXRD analysis experimental (calculated): 10.138 (10.283), 15.291 (15.607), 17.438 (17.791), 21.166 (21.685), 31.407 (31.738), 32.650 (32.729).

Example 35

Carbamazepine:1,3,5,7-adamantane tetracarboxylic acid (1:1 stoichiometry)

15 mg (0.1524 mmol) carbamazepine and 20 mg (0.1556 mmol) 1,3,5,7-adamantanetetracarboxylic acid were dissolved in approximately 1 mL methanol or 1

mL ethanol. Slow evaporation of the solvent yields clear plates of a 2:1 carbamazepine/1,3,5,7-adamantanetetracarboxylic acid co-crystal, as shown in Figure 56A-B.

Crystal data: (Bruker SMART-APEX CCD Diffractometer). $C_{44}H_{40}N_2O_{10}$, M=784.80, monoclinicC2/c; a=18.388(4), b=12.682(3), c=16.429(3) Å, β=100.491(6)°, V=3767.1(14) $Å^3$, T=100(2) K, Z=4, μ(MO-Kα)=0.099 mm^{-1}, D_c=1.384 Mg/m^3, λ=0.71073Å, F(000)1648, $2\theta_{max}$=28.20°. 16499 reflections measured, 4481 unique (R_{int}=0.052). Final residuals for 263 parameters were R_1=0.0433 and wR_2=0.0913 for I>2σ(I).

Crystal packing: The co-crystals form a single 3D network of four tetrahedron, linked by square planes similar to the *PtS* topology. The crystals are sustained by hydrogen bonding.

Infrared Spectroscopy: (Nicolet Avatar 320 FTIR). 3431 cm^{-1}, (N-H stretch, 1° amine, CBZ); 3123 cm^{-1}, (C-H stretch, alkene); 1723 cm^{-1}, (C=O); 1649 cm^{-1}, (C=C).

Melting Point: (MEL-TEMP). 258-260 degrees C (carbamazepine m.p. = 191-192 degrees C, adamantanetetracarboxylic acid m.p. = >390 degrees C).

Thermogravimetric Analysis: (TA Instruments 2950 Hi-Resolution TGA). 9% weight loss starting at 189 degrees C, a 52% weight loss starting at 251 degrees C and a 31% weight loss starting at 374 degrees C followed by complete decomposition.

Example 36

Carbamazepine:benzoquinone (1:1 stoichiometry)

25 mg (0.1058 mmol) carbamazepine and 11 mg (0.1018 mmol) benzoquinone was dissolved in 2 mL methanol or THF. Slow evaporation of the solvent produced an average yield of yellow crystals of a 1:1 carbamazepine/benzoquinone co-crystal, as shown in Figure 57A-B.

Crystal data: (Bruker SMART-APEX CCD Diffractometer). $C_{21}H_{16}N_2O_3$, M=344.36, monoclinic P2(1)/c; a=10.3335(18), b=27.611(5), c=4.9960(9) Å, β=102.275(3)°, V=1392.9(4) $Å^3$, T=100(2) K, Z=3, D_c=1.232 Mg/m^3, μ(MO-Kα)=0.084 mm^{-1}, λ=0.71073Å, F(000)540, $2\theta_{max}$=28.24°. 8392 reflections measured,

3223 unique (R_{int}=0.1136). Final residuals for 199 parameters were R_1=0.0545 and wR_2=0.1358 for I>2σ(I), and R_1=0.0659 and wR_2=0.1427 for all 3223 data.

Crystal packing: The co-crystals contain hydrogen bonded carboxamide homodimers. Each 1° amine on the CBZ is bifurcated to a carbonyl group of a benzoquinone moiety. The dimers form infinite chains.

Infrared Spectroscopy: (Nicolet Avatar 320 FTIR). 3420 cm^{-1}, (N-H stretch, 1° amine, CBZ); 2750 cm^{-1}, (aldehyde stretch); 1672 cm^{-1}, (C=O); 1637 cm^{-1}, (C=C, CBZ).

Melting Point: 170 degrees C (MEL-TEMP). (carbamazepine m.p. = 191-192 degrees C, benzoquinone m.p. = 115.7 degrees C).

Thermogravimetric Analysis: (TA Instruments 2950 Hi-Resolution TGA). 20.62% weight loss starting at 168 degrees C and a 78% weight loss starting at 223 degrees C followed by complete decomposition.

Example 37

Carbamazepine:trimesic acid (Form II) (1:1 stoichiometry)

36 mg (0.1524 mmol) carbamazepine and 31 mg (0.1475 mmol) trimesic acid were dissolved in a solvent mixture of approximately 2 mL methanol and 2 mL dichloromethane. Slow evaporation of the solvent mixture yielded white starbursts of a 1:1 carbamazepine/trimesic acid co-crystal, as shown in Figure 58A-B.

Crystal data: (Bruker SMART-APEX CCD Diffractometer). $C_{24}H_{18}N_2O_7$, M=446.26, monoclinic C2/c; a=32.5312(50), b=5.2697(8), c=24.1594(37) Å, α=90°, β=98.191(3)°, γ=90°, V=4099.39(37) $Å^3$, T=-173 K, Z=8, μ(MO-Kα)=0.110 mm^{-1}, D_c=1.439 Mg/m^3, λ=0.71073Å, F(000)1968, $2\theta_{max}$=26.43°. 11581 reflections measured, 4459 unique (R_{int}=0.0611). Final residuals for 2777 parameters were R_1=0.1563, wR_2=0.1887 for I>2σ(I), and R_1=0.1441, wR_2=0.1204 for all 3601 data.

Crystal packing: The co-crystals are sustained by hydrogen bonded carboxylic acid homodimers between carbamazepine and trimesic acid moieties and hydrogen bonded carboxylic acid-amine heterodimers between two trimesic acid moieties arranged in a stacked ladder formation.

Infrared Spectroscopy: (Nicolet Avatar 320 FTIR). 3486 cm^{-1}(N-H stretch, 1° amine, CBZ); 1688 cm^{-1} (C=O, 1° amide stretch, CBZ); 1602 cm^{-1} (C=C, CBZ).

Differential Scanning Calorimetry: (TA Instruments 2920 DSC). 273 degrees C (endotherm). m.p. = NA, decomposes at 278 degrees C (MEL-TEMP). (carbamazepine m.p. = 191-192 degrees C, trimesic acid m.p. = 380 degrees C)

Thermogravimetric Analysis: (TA Instruments 2950 Hi-Resolution TGA). 62.83% weight loss starting at 253 degrees C and a 30.20% weight loss starting at 278 degrees C followed by complete decomposition.

Powder x-ray diffraction: (Rigaku Miniflex Diffractometer using CuKα (λ=1.540562), 30kV, 15mA). The powder data were collected over an angular range of 3 to 40 2 in continuous scan mode using a step size of 0.02 2 and a scan speed of 2.0 /min. PXRD analysis experimental: 10.736, 12.087, 16.857, 24.857, 27.857.

Table V. Detailed Characterization of Co-Crystals

All PXRD peaks are in units of degrees 2-theta
All Raman shifts are in units of cm^{-1}

Carbamazepine: Saccharin PXRD (Form I): 7.01, 12.07, 14.09, 15.41, 18.47, 20.13, 22.01, 23.57, 24.41, 28.31 (Fig. 1) PXRD (Form II): 6.9, 12.2, 13.6, 14.0, 14.1, 15.3, 15.9, 18.1, 18.7, 20.2, 21.3, 23.7, 26.3, 28.3 DSC (Form I): Broad endotherm at 161.9 degrees C (Fig. 2) TGA (Form I): Decomposition above 200 degrees CDSC (Form II): Endothermic transitions at 75.31 and 177.32 degrees C TGA (Form II): 3.342 percent weight loss starting at 67.03 degrees C, 55.09 percent weight loss starting at 118.71 degrees C, followed by decomposition Method: CMAX
Carbamazepine: Nicotinamide PXRD (Form I): 4.97, 6.67, 8.75, 10.25, 13.25, 17.91, 18.49, 19.95, 20.49, 22.73, 24.39, 26.49 (Fig. 3) PXRD (Form II): 6.5, 8.8, 10.1, 13.2, 15.6, 17.7, 17.8, 18.3, 19.8, 20.4, 21.6, 22.6, 22.9, 26.4, 26.7, 28.0 DSC (Form I): Sharp endotherm at 156.9 degrees C (Fig. 4) TGA (Form I): Decomposition beginning at ~150 degrees CDSC (Form II): Endothermic transitions at 74.49 and 159.05 degrees C TGA (Form II): 57.94 percent weight loss starting at 205.43 degrees C, followed by decomposition Method: CMAX
Carbamazepine: Trimesic acid PXRD (Form I): 10.89, 12.23, 14.83, 16.25, 17.05, 18.13, 18.47, 21.47, 21.95, 24.57, 25.11, 27.99 (Fig. 5) PXRD (Form II): 10.74, 12.09, 16.86, 24.86, 27.86 DSC (Form II): Endothermic transition at 273 degrees C TGA (Form II): 62.83 percent weight loss starting at 253 degrees C, 30.20 percent

weight loss starting at 278 degrees C, followed by decomposition Method: CMAX
Celecoxib: Nicotinamide PXRD: 3.77, 7.56, 9.63, 14.76, 15.21, 16.01, 17.78, 18.68, 19.31, 20.44, 21.19, 22.10 DSC: Two endothermic transitions at 117.2 and 118.8 degrees C and a sharp endotherm at 129.7 degrees C TGA: Decomposition beginning at ~150 degrees C Raman: 1617.5, 1598.7, 1452.1, 1370.3, 1162.5, 1044.3, 972.9, 796.4, 631.8, 392.5, 205.9 Method: Slow evaporation of a 1:1 solution from acetone
Topiramate: 18-Crown-6 PXRD: 10.79, 11.07, 12.17, 13.83, 16.13, 18.03, 18.51, 18.79, 19.21, 21.43, 22.25, 24.11 (Fig. 6) DSC: Sharp endotherm at 134.7 degrees C, followed by an exotherm at 203 degrees C (Fig. 7) TGA: Rapid decomposition beginning at ~ 135 degrees C and leveling off slightly after 200 degrees C Raman: 2994.5, 2942.7, 1471.6, 1427.4, 1261.7, 849.4, 804.5, 745.1, 629.2, 280.4, 225.9 Method: Addition of an ether solution containing 1 equivalent of topiramate to an ether solution containing 18-crown-6. Product precipitated following minor agitation of the combined mixture and was collected.
Olanzapine: Nicotinamide PXRD (Form I): 4.89, 8.65, 12.51, 14.19, 15.59, 17.15, 19.71, 21.05, 23.95, 24.59, 25.53, 26.71 (Fig. 8) PXRD (Form II): 6.41, 12.85, 18.67, 21.85, 24.37 (Fig.30) PXRD (Form III): 6.41, 12.85, 14.91, 18.67, 21.85, 24.37 (Fig. 31) DSC (Form I): Slightly broad endotherm at 126.1 degrees C (Fig. 9) Method: See above
Celecoxib: 18-Crown-6 PXRD: 8.73, 11.89, 12.57, 13.13, 15.01, 16.37, 17.03, 17.75, 18.45, 20.75, 22.37, 23.11, 24.33, 24.97, 26.61, 28.15 (Fig. 10) DSC: Sharp endotherm at 189.6 degrees C (Fig. 11) TGA: Decomposition above 200 degrees C with a 25% weight loss between ~190-210 degrees C Method: A solution containing one equivalent of celecoxib in ether was added to a solution containing 18-crown-6. A white solid formed immediately and was collected.
Itraconazole: Succinic Acid PXRD: 3.0, 6.0, 8.1, 9.0, 17.1, 24.5 (Fig. 12) DSC: Single endothermic transition at 160.1 degrees C ± 1.0 degrees C (Fig. 13) TGA: Less than 0.1 % volatile components by weight Method: See above
Itraconazole: Fumaric Acid PXRD: 4.6, 5.9, 9.2, 10.6, 19.1, 20.8 (Fig. 14) DSC: The material had a weak endothermic transition at 141.7 degrees C and a strong endothermic transition at 179.58 degrees C (Fig. 15) TGA: The sample loses 0.5 % of its weight on the TGA between room temperature and 100 degrees C Method:

Itraconazole: Tartaric Acid PXRD: 4.1, 6.2, 8.3, 20.7, 25.6, 26.3 (Fig. 16) DSC: An endothermic transition at 180.74 degrees C (Fig. 17) TGA: Less than 0.1 % volatile components by weight by TGA. Method: See above
Itraconazole: Malic acid PXRD: 4.4, 5.9, 8.8, 17.7, 20.0, 21.1, 22.6 (Fig. 18) DSC: The sample has a strong endothermic transition at 154.36 degrees C (Fig.19) TGA: The sample contained less than 0.1% volatile components by weight Method: See above
ItraconazoleHCl: Tartaric acid PXRD: 3.7, 11.0, 13.8, 16.5, 17.8 (Fig. 20) DSC: The sample has a peak endothermic transition at 161degrees C (Fig. 21) TGA: The sample contained less than 0.1 % volatile components by weight Method: See above
Modafinil: Malonic acid PXRD: 5.00, 9.17, 16.81, 18.26, 19.43, 21.36, 21.94, 22.77, 24.49, 25.63, 28.45 (Fig. 22) DSC: Endothermic transition at 106.23 degrees C (Fig. 40) Raman: 1601, 1183, 1032, 1004, 814, 633, 265, 222 (Fig. 42) Method: See above
Modafinil: Benzamide PXRD: 5.11, 9.35, 10.25, 10.79, 14.07, 16.87, 18.33, 19.53, 21.38, 22.05, 22.89, 23.57, 24.73, 25.19, 25.81, 26.51, 28.60 (Fig. 23) Method: Slow evaporation from a 1:1 solution in 1,2-dichoroethane
Modafinil: Mandelic acid PXRD: 6.11, 6.75, 9.53, 10.31, 14.77, 15.77, 16.99, 18.03, 20.01, 21.61, 22.47, 23.27, 25.27, 25.75, 27.23 (Fig. 24) Method: Slow evaporation from a 1:1 solution in acetone
Modafinil: Glycolic acid PXRD: 6.09, 9.51, 14.91, 15.97, 19.01, 20.03, 21.59, 22.43, 22.75, 23.75, 25.03, 25.71 (Fig. 25) Method: Slow evaporation from a 1:1 solution in acetone
Modafinil: Fumaric acid PXRD: 5.87, 7.19, 8.95, 12.49, 13.99, 16.13, 17.09, 18.19, 19.99, 21.57, 23.48, 25.01, 25.79, 28.17, 28.87, 29.69, 32.19 (Fig. 26) Method: Slow evaporation from a 1:1 solution in 1,2-dichoroethane
Modafinil: Maleic acid PXRD: 4.69, 6.15, 9.61, 10.23, 15.65, 16.53, 17.19, 18.01, 19.27, 19.53, 19.97, 21.83, 22.45, 25.65 (Fig. 43) Method: See above
5-fluorouracil: Urea PXRD: 11.23, 12.69, 13.27, 15.93, 16.93, 20.37, 23.65, 25.55, 26.87, 32.49 (Fig. 36) DSC: Sharp endotherm at 207.6 degrees C (Fig. 33) TGA: 32 percent weight loss between 150 and 220 degrees C (Fig. 34) Raman: 1347.1, 1024.4, 756.9, 643.7, 545.3 (Fig. 35) Method: See above
Hydroclorothiazide: Nicotinic acid PXRD: 8.57, 13.23, 14.31, 16.27, 17.89, 18.75, 21.13, 21.45, 24.41, 25.73, 26.57, 27.43 (Fig. 37)

Method: See above
Hydrochlorothiazide: 18-crown-6 PXRD: 9.97, 10.43, 11.57, 11.81, 12.83, 14.53, 15.67, 16.61, 19.05, 20.31, 20.65, 21.09, 21.85, 22.45, 23.63, 24.21, 25.33, 26.73 (Fig. 38) Method: See above
Hydrochlorothiazide: piperazine PXRD: 6.85, 13.75, 15.93, 18.71, 20.67, 20.93, 23.27, 24.17, 28.33, 28.87, 30.89 (Fig. 39) Method: See above
Acetaminophen: 4,4'-bipyridine:water DSC: Endothermic transition at 57.77 degrees C Method: See above
Phenytoin: Pyridone PXRD: 5.2, 11.1, 15.1, 16.2, 16.7, 17.8, 19.4, 19.8, 20.3, 21.2, 23.3, 26.1, 26.4, 27.3, 29.5 DSC: Endothermic transitions at 233.39 and 271.33 degrees C TGA: 29.09 percent weight loss starting at 192.8 degrees C, 48.72 percent weight loss starting at 238.27 degrees C, 18.38 percent weight loss starting at 260.17 degrees C, followed by decomposition Method: See above
Aspirin: 4,4'-bipyridine DSC: Endothermic transition at 95.14 degrees C TGA: 9 percent weight loss starting at 22.62 degrees C, 49.06 percent weight loss starting at 102.97 degrees C, decomposition starting at 209.37 degrees C Method: See above
Ibuprofen: 4,4'-bipyridine PXRD: 3.4, 6.9, 10.4, 17.3, 19.1 DSC: Endothermic transitions at 64.85 and 118.79 degrees C TGA: 13.28 percent weight loss between room temperature and 100.02 degrees C followed by decomposition Method: See above
Flurbiprofen: 4,4'-bipyridine PXRD: 16.8, 17.1, 18.1, 19.0, 20.0, 21.3, 22.7, 25.0, 26.0, 26.0, 26.1, 28.2, 29.1 DSC: Endothermic transition at 162.47 degrees C TGA: 30.93 percent weight loss starting at 31.13 degrees C, 46.26 percent weight loss starting at 168.74 degrees C, followed by decomposition Method: See above
Flurbiprofen:trans-1,2-bis (4-pyridyl) ethylene PXRD: 3.6, 17.3, 18.1, 18.4, 19.1, 22.3, 23.8, 25.9, 28.1 DSC: Endothermic transitions at 100.01, 125.59, and 163.54 degrees C TGA: 91.79 percent weight loss starting at 133.18 degrees C followed by decomposition Method: See above
Carbamazepine: p-phthalaldehyde PXRD: 8.5, 10.6, 11.9, 14.4, 15.1, 18.0, 18.5, 19.8, 23.7, 24.2, 26.4, 27.6, 27.8, 28.7, 29.3, 29.4 DSC: Endothermic transition at 128.46 degrees C TGA: 17.66 percent weight loss starting at 30.33 degrees C, 17.57 percent weight loss starting at 100.14 degrees C, followed by decomposition Method: See above

Carbamazepine: 2,6-pyridinecarboxylic acid TGA: 69 percent weight loss starting at 215 degrees C, 17 percent weight loss starting at 392 degrees C, followed by decomposition Method: See above
Carbamazepine: 5-nitroisophthalic acid PXRD: 10.14, 15.29, 17.44, 21.17, 31.41, 32.65 TGA: 32.02 percent weight loss starting at 202 degrees C, 12.12 percent weight loss starting at 224 degrees C, 17.94 percent weight loss starting at 285 degrees C, followed by decomposition Method: See above
Carbamazepine: 1,3,5,7-adamantane tetracarboxylic acid TGA: 9 percent weight loss starting at 189 degrees C, 52 percent weight loss starting at 251 degrees C, 31 percent weight loss starting at 374 degrees C, followed by decomposition Method: See above
Carbamazepine: Benzoquinone TGA: 20.62 percent weight loss starting at 168 degrees C, 78 percent weight loss starting at 223 degrees C, followed by decomposition Method: See above

Example 38

A co-crystal with a modulated dissolution profile has been prepared. Celecoxib: nicotinamide co-crystals were prepared via methods shown in example 4. (See Fig. 27)

Example 39

A co-crystal with a modulated dissolution profile has been prepared. Itraconazole: succinic acid, itraconazole:tartaric acid and itraconazole:malic acid co-crystals were prepared via methods shown in examples 8, 10 and 11. (See Fig. 28)

Example 40

A co-crystal of an unsaltable or difficult to salt API has been prepared. Celecoxib: nicotinamide co-crystals were prepared via methods shown in example 4.

Example 41

A co-crystal with an improved hygroscopicity profile has been prepared. Celecoxib: nicotinamide co-crystals were prepared via methods shown in example 4. (See Fig. 29)

Example 42

A co-crystal with reduced form diversity as compared to the API has been prepared.

Co-crystals of carbamazepine and saccharin have been prepared via method shown in example 1.

TABLE I

Co-Crystal Former	MW (g/mol)	MP (°C)	Class	Functionality	# acceptors	# donors	Molecular Structure	pKa Values
1-Hydroxy-2-naphthoic acid	188.18	191-192	2	Carboxylic acid, alcohol	1	2		2.7, 13.5
4-aminobenzoic acid	137.14	187-188	2	Amine, carboxylic acid	1	3		4.7, 4.8
4-aminopyridine	94.11	158-159	3	Amine, pyridine	1	2		10
4-Chlorobenzene-sulfonic acid	192.63	67	1	SO_3H	3	1		0-1
4-ethoxyphenyl urea	180.2	173-174	3	Amide, NH	2	3		~7-9
7-oxo-DHEA	303	190-192	1	Alcohol, Ketone	3	1		

TABLE I

Co-Crystal Former	MW (g/mol)	MP (°C)	Class	Functionality	# acceptors	# donors	Molecular Structure	pKa Values
Acesulfame	163.15	123-124	3	SO_2, Amide	4	1		~5-7
Acetohydroxamic acid	75.07	89-92	3	Amide, NH, OH	2	2		8.7
Adenine	135.13	220 (sub.)	1	Amine, NH	3	3		3.8
Adipic Acid	146.14	152	1	Carboxylic acid	2	2	$HOOC(CH_2)_4COOH$	4.44, 5.44
Alanine	89.09	289-291	1	Amine, carboxillic acid	1	3		2.35, 9.87
Allopurinaol	136.11	> 350	3	OH, NH	4	2		10.2

TABLE I

Co-Crystal Former	MW (g/mol)	MP (°C)	Class	Functionality	# acceptors	# donors	Molecular Structure	pKa Values
Arginine	174.2	244 (dec.)	1	Amine, COOH	2	7		2.18, 9.09, 13.2
Ascorbic acid	176.12	190-192	1	C=O, OH	6	4		4.17, 11.57
Asparagine	132.12	234-235	1	Amine, amide, COOH	3	5		2.02, 8.5
Aspartic acid	133.1	270-271	1	Amine, COOH	2	4		1.88, 3.65, 9.60
Benzenesulfonic Acid	158.18	43-44	1	SO_3H	2	1		0.70, 1.58
Benzoic acid*	122.12	122-123	2	COOH	1	1		4.19

TABLE I

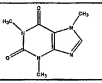
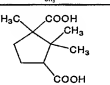
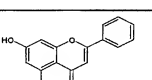
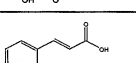
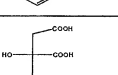
Co-Crystal Former	MW (g/mol)	MP (°C)	Class	Functionality	# acceptors	# donors	Molecular Strucutre	pKa Values
Caffeine	194.19	238	3	C=O	3	0		
Camphoric acid	200.23	186-189	2	Carboxylic acid	2	2		4.72, 5.83
Capric acid	172.27	31.4	1	Carboxylic acid	1	1	$CH_3(CH_2)_8COOH$	4.9
Chrysin	254.24	285	1	Phenol, ether, ketone	2	2		
Cinnamic acid	144.2	133	3	Carboxylic acid	1	1		4.4
Citric Acid	192.12	153	1	OH, COOH	4	4		3.13, 4.76, 6.40

TABLE I

Co-Crystal Former	MW (g/mol)	MP (°C)	Class	Functionality	# acceptors	# donors	Molecular Structure	pKa Values
Clemizole	325.84	167	1	Pyrrolidine	3	0		
Cyclamic acid	179.24	169-170	3	NH, SO_3H	2	2		-2
Cysteine	121.15	----	1	Amine, COOH, SH	2	4		1.71, 8.33, 10.78
Dimethylglycine	103.1	178-192	1	Amine, Carboxylic acid	2	1		2.5
D-Ribose	150.13	87	1	Alcohol, ether	1	4		
Fumaric acid	116.07	287	1	COOH	2	2		3.03, 4.38

TABLE I

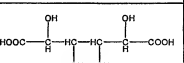
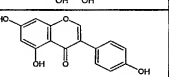
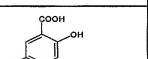
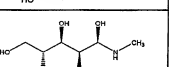
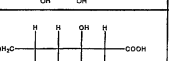
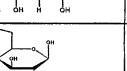
Co-Crystal Former	MW (g/mol)	MP (°C)	Class	Functionality	# acceptors	# donors	Molecular Strucutre	pKa Values
Galactaric acid	210.14	255 (dec)	1	Carboxylic acid, alcohol	2	6		3.08, 3.63
Genistein	270.24	297-298	1	Alcohol, Phenol, ether, ketone	2	3		
Gentisic acid	154.12	199-200 form I, 205 form II	2	Carboxylic acid, alcohol, phenol	1	3		2.93
Glucamine, N-Methyl	195.22	128-129	1	Alcohol, Amine	5	6		8.03(B)
Gluconic acid	196.15	131	1	OH, COOH	6	6		3.76
Glucosamine	179.17	88	1	OH	5	6		6.91

TABLE I

Co-Crystal Former	MW (g/mol)	MP (°C)	Class	Functionality	# acceptors	# donors	Molecular Structure	pKa Values
Glucuronic acid	194.14	165	1	Carboxylic acid, alcohol, aldehyde	2	5		3.18
Glutamic acid	147.13	160	1	Amine, COOH	2	4		2.19, 4.25, 9.67
Glutamine	146.15	185-186	1	Amine, Amide, COOH	2	5		2.17, 9.13
Glutaric acid	132.11	98-98	1	COOH	2	2		2.7, 4.5
Glycine	75.07	182	1	Amine, COOH	2	3		2.34, 9.6
Glycolic acid	76.05	80	1	OH, COOH	2	2		3.82

TABLE I

Co-Crystal Former	MW (g/mol)	MP (°C)	Class	Functionality	# acceptors	# donors	Molecular Structure	pKa Values
Hippuric acid	179.17	187-188	1	Amide, NH, COOH	2	2		3.55
Histidine	155.16	287 (dec.)	1	Amine, COOH, Imidazole	2	4		1.78, 6.97, 8.97
Hydroquinone*	110.11	170-171	2	OH, Phenol	2	2		~10
Imidazole	68.08	90-91	1	NH	1	1		6.92
Ipriflavone	280.32	115-117	1	Ketone, ether	3	0		
Isoleucine	131.17	168-170 (sub.)	1	Amine, COOH	1	3		2.32, 9.76

TABLE I

Co-Crystal Former	MW (g/mol)	MP (°C)	Class	Functionality	# acceptors	# donors	Molecular Structure	pKa Values
Lactobionic acid	358.3	128-130	2	Alcohol, carboxylic acid, ether	1	9		3.2
Lauric acid	200.32	44-48	1	Carboxylic acid	1	1	$CH_3(CH_2)_{10}COOH$	~4.5
Leucine	131.17	145-148 (sub.)	1	Carboxylic acid, amine	1	3		2.36, 9.6
Lysine	146.19	225 (dec.)	1	Amine, COOH	1	5		2.2, 8.9, 10.28
Maleic	116.07	138-139	1	COOH	2	2		1.92, 6.23
Malic acid	134.09	131-132	1	OH, COOH	3	3		3.46, 5.1

TABLE I

Co-Crystal Former	MW (g/mol)	MP (°C)	Class	Functionality	# acceptors	# donors	Molecular Structure	pKa Values
Malonic	104.06	135	1	COOH	2	2		2.83, 5.70
Mandelic acid	152.15	119	1	OH, COOH	2	2		3.37
Methionine	149.21	280-282 (dec.)	1	Amine, COOH, S-Me	2	3		2-3, 9
Nicotinamide	122.12	128-131	1	Pyridine, amide	2	2		3.3
Nicotinic acid	123.11	236-237	2	Carboxylic acid, pyridine	2	1		2.07(B), 4.85
Orotic acid	156.1	345-346	2	Carboxilic acid, lactam	3	3		5.85, 8.95

TABLE I

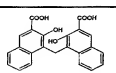
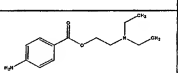
Co-Crystal Former	MW (g/mol)	MP (°C)	Class	Functionality	# acceptors	# donors	Molecular Strucutre	pKa Values
Oxalic acid	90.04	189 (dec)	2	Carboxilic acid	2	2		1.27, 4.27
Palmitic acid	256.43	63-64	1	Carboxylic acid	1	1	$CH_3(CH_2)_{14}COOH$	4.9
Pamoic	388.38	280 (dec)	2	Carboxylic acid, phenol	2	4		2.51, 3.1
Phenylalanine	165.19	283 (dec.)	1	Amine, COOH	1	3		~2, ~9
Piperazine	86.14	106	1	NH	0	2		9.82(B)
Procaine	236.31	61	1	Amine, C=O	2	2		8.9(B)
Proline	115.13	220-222 (dec.)	1	COOH, NH	1	2		1.99, 10.6

TABLE I

Co-Crystal Former	MW (g/mol)	MP (°C)	Class	Functionality	# acceptors	# donors	Molecular Strucutre	pKa Values
p-Toluenesulfonic acid	172.2	106-107	2	Sulfonic acid	2	1		-1.34
Pyridoxamine	168	193-194	2	OH, Amine, Pyridine	3	4		~9
Pyridoxine	170	160	2	Alcohol, Pyridine	3	3		~9
Pyroglutamic acid	129.12	162	2	Carboxylic acid, Lactam	2	2		3.32
Quercetin	302.24	314 dec.	1	Phenol, ether, ketone	2	5		
Resveratrol	228.24	253-255	1	Phenol	0	3		

TABLE I

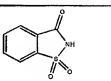
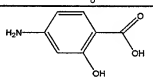
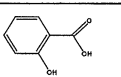
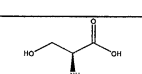
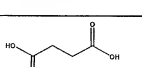
Co-Crystal Former	MW (g/mol)	MP (°C)	Class	Functionality	# acceptors	# donors	Molecular Strucutre	pKa Values
Saccharin	183.19	228-230	1	Amide, C=O, S=O, N-H	3	1		2
Salicylic acid, 4-amino	153.14	150-151	3	COOH, OH, Analine	1	4		3.25, 10, 3.5(B)
Salicylic acid	138.12	159	3	COOH, OH	2	2		2.98, 13.82
Sebacic acid	202.25	134.5	1	Carboxylic acid	2	2	$HOOC(CH_2)_8COOH$	4.59, 5.59
Serine	105.09	228 (dec.)	1	Carboxylic acid, amine, OH	2	3		2.21, 9.15
Stearic acid	284.47	70-71	1	Carboxylic acid	1	1	$CH_3(CH_2)_{16}COOH$	4.9
Succinic acid	118.09	185-187	1	Carboxylic acid	2	2		4.21, 5.64

TABLE I

Co-Crystal Former	MW (g/mol)	MP (°C)	Class	Functionality	# acceptors	# donors	Molecular Structure	pKa Values
Tartaric acid	150.09	205-206	1	Carboxylic acid	4	4		3.02, 4.36
Threonine	119.12	255-257 (dec.)	1	Amine, COOH, OH	2	4		2.15, 9.12
TRIS	121.13	171-172	2	Amine, OH	3	5		5.81, 8.3
Tryptophan	204.23	289 (dec.)	1	Amine, COOH, Indole	1	4		2.38, 9.39
Tyrosine	181.19	342-344	1	Amine, COOH, OH	2	3		2.2, 9.11, 10.07
Urea	60.06	Dec.	1	C=O, NH2	1	4		~8

TABLE I

Co-Crystal Former	MW (g/mol)	MP (°C)	Class	Functionality	# acceptors	# donors	Molecular Structure	pKa Values
Valine	117.15	315	1	Amine, COOH	1	3		~4.5, ~9
Vitamin K5	209.68	280-282 (dec.)	3	Amine, OH	1	3		~9
Xylitol	152.15	93-95 (I)	2	OH	5	5		~9

TABLE II

Co-crystal Former	Co-crystal Former Functional Group	Interacting Group							
1,5-Napthalene-disulfonic Acid	Sulfonic Acid	pyridine	ketone	aldehyde	ether	ester	amide	Carboxylic Acid
1-Hydroxy-2-naphthoic acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
1-Hydroxy-2-naphthoic acid	alcohol	alcohol	ketone	thiol	amide	amine	analine	phenol
4-Aminobenzoic Acid	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol
4-Aminobenzoic Acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
4-aminopyridine	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol
4-aminopyridine	Pyridine	*alcohol	pyridinium	*	*amide	nitro	*amine	*Carboxylic Acid
4-Chlorobenzene-Sulfonic Acid	Sulfonic Acid	pyridine	ketone	aldehyde	ether	ester	amide	Carboxylic Acid
4-ethoxyphenyl Urea	Amide	alcohol	ketone	thiol	amide	amine	analine	phenol
4-ethoxyphenyl Urea	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol
7-oxo-DHEA	alcohol	alcohol	ketone	thiol	amide	amine	analine	phenol
7-oxo-DHEA	Ketone	alcohol	ketone	thiol	amide	amine	analine	phenol
Acesulfame	Sulfone	pyridine	ketone	aldehyde	ether	ester	amide	carboxilic acid
Acesulfame	Amide	alcohol	ketone	thiol	amide	amine	analine	phenol
Acetohydroxamic Acid	Amide	alcohol	ketone	thiol	amide	amine	analine	phenol
Acetohydroxamic Acid	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol
Acetohydroxamic Acid	Alcohol	alcohol	ketone	thiol	amide	amine	analine	phenol
Adenine	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol
Adenine	N	*alcohol	pyridinium	*	*amide	nitro	*amine	*carboxilic acid
Adipic acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Alanine	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol
Alanine	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Allopurinaol	Alcohol	alcohol	ketone	thiol	amide	amine	analine	phenol
Allopurinaol	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol
Arginine	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol
Arginine	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Ascorbic Acid	Ketone	alcohol	ketone	thiol	amide	amine	analine	phenol
Ascorbic Acid	Alcohol	alcohol	ketone	thiol	amide	amine	analine	phenol
Ascorbic Acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol

TABLE II

Co-crystal Former									
1,5-Napthalene-disulfonic Acid	amine	metals	thioether		sulfate	alcohol			
1-Hydroxy-2-naphthoic acid	phosphate	sulfate	sulfone	nitrate	pyridine	carboxilic acid	metals		aldehyde
1-Hydroxy-2-naphthoic acid	phosphate	sulfate	sulfone	nitrate	pyridine	carboxilic acid	metals		aldehyde
4-Aminobenzoic Acid	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid		metals
4-Aminobenzoic Acid	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid		metals
4-aminopyridine	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid		metals
4-aminopyridine	*sulfonamide	*ketone	ether	triazole		ammonium	oxime	*chlorine	
4-Chlorobenzene-Sulfonic Acid	amine	metals	thioether		sulfate	alcohol			
4-ethoxyphenyl Urea	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid		metals
4-ethoxyphenyl Urea	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid		metals
7-oxo-DHEA	phosphate	sulfate	sulfone	nitrate	pyridine	carboxilic acid	metals		aldehyde
7-oxo-DHEA	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid		metals
Acesulfame	amine	metals	thioether		sulfate	alcohol			
Acesulfame	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid		metals
Acetohydroxamic Acid	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid		metals
Acetohydroxamic Acid	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid		metals
Acetohydroxamic Acid	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid		metals
Adenine	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid		metals
Adenine	*sulfonamide	*ketone	ether	triazole		ammonium	oxime		*chlorine
Adipic acid	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid		metals
Alanine	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid		metals
Alanine	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid		metals
Allopurinaol	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid		metals
Allopurinaol	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid		metals
Arginine	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid		metals
Arginine	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid		metals
Ascorbic Acid	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid		metals
Ascorbic Acid	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid		metals
Ascorbic Acid	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid		metals

TABLE II

Co-crystal Former								
1,5-Napthalene-disulfonic Acid								
1-Hydroxy-2-naphthoic acid	ester	ether	cyano		furan	bromine	chlorine	s-heterocyclic
1-Hydroxy-2-naphthoic acid	ester	ether	cyano		furan	bromine	chlorine	s-heterocyclic
4-Aminobenzoic Acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
4-Aminobenzoic Acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
4-aminopyridine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
4-aminopyridine		thiol	n-heterocyclic ring	thionedisulfide	pyrrolidindione	iodine	hydrazone	thiocyanate
4-Chlorobenzene-Sulfonic Acid								
4-ethoxyphenyl Urea	aldehyde	ester	ether	cyano		furan	bromine	chlorine
4-ethoxyphenyl Urea	aldehyde	ester	ether	cyano		furan	bromine	chlorine
7-oxo-DHEA	ester	ether	cyano		furan	bromine	chlorine	s-heterocyclic
7-oxo-DHEA	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Acesulfame								
Acesulfame	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Acetohydroxamic Acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Acetohydroxamic Acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Acetohydroxamic Acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Adenine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Adenine		thiol	n-heterocyclic ring	thionedisulfide	pyrrolidindione	iodine	hydrazone	thiocyanate
Adipic acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Alanine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Alanine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Allopurinaol	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Allopurinaol	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Arginine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Arginine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Ascorbic Acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Ascorbic Acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Ascorbic Acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine

TABLE II

Co-crystal Former							
1,5-Naphthalene-disulfonic Acid							
1-Hydroxy-2-naphthoic acid	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		fluorine
1-Hydroxy-2-naphthoic acid	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		fluorine
4-Aminobenzoic Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
4-Aminobenzoic Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
4-aminopyridine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
4-aminopyridine	*bromine		hydroxamic acid	cyano	carboxamide	*sulfonic acid	*phosphoric acid
4-Chlorobenzene-Sulfonic Acid							
4-ethoxyphenyl Urea	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
4-ethoxyphenyl Urea	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
7-oxo-DHEA	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		fluorine
7-oxo-DHEA	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Acesulfame							
Acesulfame	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Acetohydroxamic Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Acetohydroxamic Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Acetohydroxamic Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Adenine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Adenine	*bromine		hydroxamic acid	cyano	carboxamide	*sulfonic acid	*phosphoric acid
Adipic acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Alanine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Alanine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Allopurinaol	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Allopurinaol	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Arginine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Arginine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Ascorbic Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Ascorbic Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Ascorbic Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	

TABLE II

Co-crystal Former								
1,5-Napthalene-disulfonic Acid								
1-Hydroxy-2-naphthoic acid	carbamate	imidazole	BF4					
1-Hydroxy-2-naphthoic acid	carbamate	imidazole	BF4					
4-Aminobenzoic Acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
4-Aminobenzoic Acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
4-aminopyridine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
4-aminopyridine	N-oxide	ester	ether	fluorine	acetate	thione	dithiadiazocyclopentadienyl	
4-Chlorobenzene-Sulfonic Acid								
4-ethoxyphenyl Urea	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
4-ethoxyphenyl Urea	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
7-oxo-DHEA	carbamate	imidazole	BF4					
7-oxo-DHEA	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Acesulfame								
Acesulfame	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Acetohydroxamic Acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Acetohydroxamic Acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Acetohydroxamic Acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Adenine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Adenine	N-oxide	ester	ether	fluorine	acetate	thione	dithiadiazocyclopentadienyl	
Adipic acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Alanine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Alanine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Allopurinaol	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Allopurinaol	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Arginine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Arginine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Ascorbic Acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Ascorbic Acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Ascorbic Acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea

TABLE II

Co-crystal Former			
1,5-Naphtalene-disulfonic Acid			
1-Hydroxy-2-naphthoic acid			
1-Hydroxy-2-naphthoic acid			
4-Aminobenzoic Acid	iodine		
4-Aminobenzoic Acid	iodine		
4-aminopyridine	iodine		
4-aminopyridine			
4-Chlorobenzene-Sulfonic Acid			
4-ethoxyphenyl Urea	iodine	epoxide	peroxide
4-ethoxyphenyl Urea	iodine		
7-oxo-DHEA			
7-oxo-DHEA	iodine		
Acesulfame			
Acesulfame	iodine	epoxide	peroxide
Acetohydroxamic Acid	iodine	epoxide	peroxide
Acetohydroxamic Acid	iodine		
Acetohydroxamic Acid	iodine	epoxide	
Adenine	iodine		
Adenine			
Adipic acid	iodine		
Alanine	iodine		
Alanine	iodine		
Allopurinaol	iodine	epoxide	
Allopurinaol	iodine		
Arginine	iodine		
Arginine	iodine		
Ascorbic Acid	iodine		
Ascorbic Acid	iodine	epoxide	
Ascorbic Acid	iodine		

TABLE II

Co-crystal Former	Co-crystal Former Functional Group	Interacting Group						
Asparagine	Amine	alcohol	ketone	thiol	amide	lamine	analine	phenol
Asparagine	Amide	alcohol	ketone	thiol	amide	amine	analine	phenol
Asparagine	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Aspartic Acid	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol
Aspartic Acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Benzenesulfonic Acid	Sulfonic Acid	pyridine	ketone	aldehyde	ether	ester	amide	Carboxylic Acid
Benzoic Acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Caffeine	Ketone	alcohol		thiol	amide	amine	analine	phenol
Camphoric acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Capric acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Genistein	Ketone	alcohol		thiol	amide	amine	analine	phenol
Genistein	Phenol	amine	amide	sulfoxide	n	pyridine	cyano	aldehyde
Genistein	Ether	aromatic-N	amide	amine	aromatic_s	Sp2 amine	sulfoxide	chlorate
Cinnamic acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Citric Acid	Alcohol	alcohol	ketone	thiol	amide	amine	analine	phenol
Citric Acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Clemizole	Pyrrolidine	*alcohol	pyridinium	*	*amide	nitro	*amine	*carboxilic acid
Cyclamic Acid	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol
Cyclamic Acid	Sulfonic Acid	pyridine	ketone	aldehyde	ether	ester	amide	Carboxylic Acid
Cysteine	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol
Cysteine	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Cysteine	Thiol	carboxylic acid	sodium	aldehyde	ketone	-N	cadmium	
Dimethylglycine	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Dimethylglycine	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol
D-ribose	Ether	aromatic-N	amide	amine	aromatic_s	Sp2 amine	sulfoxide	chlorate
D-ribose	Alcohol	alcohol	ketone	thiol	amide	amine	analine	phenol
Fumaric Acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Galactaric acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Galactaric acid	alcohol	alcohol	ketone	thiol	amide	amine	analine	phenol
Chrysin	Ketone	alcohol		thiol	amide	amine	analine	phenol

TABLE II

Co-crystal Former								
Asparagine	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Asparagine	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals
Asparagine	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Aspartic Acid	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Aspartic Acid	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Benzenesulfonic Acid	amine	metals	thioether		sulfate	alcohol		
Benzoic Acid	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Caffeine	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals
Camphoric acid	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Capric acid	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Genistein	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals
Genistein		alchohol		ester	ether	n-oxide	chlorine	fluorine
Genistein	chlorine		cyano	ester	amine	nitro	nitrate	bromine
Cinnamic acid	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Citric Acid	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals
Citric Acid	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Clemizole	*sulfonamide	*ketone	ether	triazole		ammonium	oxime	*chlorine
Cyclamic Acid	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Cyclamic Acid	amine	metals	thioether		sulfate	alcohol		
Cysteine	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Cysteine	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Cysteine	arsenic	chlorine	alcohol	potassium	Ru		Rb	Sb
Dimethylglycine	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Dimethylglycine	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
D-ribose	chlorine		cyano	ester	amine	nitro	nitrate	bromine
D-ribose	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals
Fumaric Acid	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Galactaric acid	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Galactaric acid	phosphate	sulfate	sulfone	nitrate	pyridine	carboxilic acid	metals	aldehyde
Chrysin	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals

TABLE II

Co-crystal Former									
Asparagine	aldehyde	ester	ether	cyano		furan	bromine	chlorine	
Asparagine	aldehyde	ester	ether	cyano		furan	bromine	chlorine	
Asparagine	aldehyde	ester	ether	cyano		furan	bromine	chlorine	
Aspartic Acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine	
Aspartic Acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine	
Benzenesulfonic Acid									
Benzoic Acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine	
Caffeine	aldehyde	ester	ether	cyano		furan	bromine	chlorine	
Camphoric acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine	
Capric acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine	
Genistein	aldehyde	ester	ether	cyano		furan	bromine	chlorine	
Genistein	bromine	iodine	ketone	sulfonic acid	sulfate	phosphate	phosphonic acid	carboxylic acid	
Genistein	aldehyde	ketone	peroxide	epoxide			heterocyclic-S	iodine	
Cinnamic acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine	
Citric Acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine	
Citric Acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine	
			n-heterocyclic						
Clemizole		thiol	ring	thionedisulfide	pyrrolidindione	iodine	hydrazone	thiocyanate	
Cyclamic Acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine	
Cyclamic Acid									
Cysteine	aldehyde	ester	ether	cyano		furan	bromine	chlorine	
Cysteine	aldehyde	ester	ether	cyano		furan	bromine	chlorine	
Cysteine									
Dimethylglycine	aldehyde	ester	ether	cyano		furan	bromine	chlorine	
Dimethylglycine	aldehyde	ester	ether	cyano		furan	bromine	chlorine	
D-ribose	aldehyde	ketone	peroxide	epoxide			heterocyclic-S	iodine	
D-ribose	aldehyde	ester	ether	cyano		furan	bromine	chlorine	
Fumaric Acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine	
Galactaric acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine	
Galactaric acid	ester	ether	cyano		furan	bromine	chlorine	s-heterocyclic	
Chrysin	aldehyde	ester	ether	cyano		furan	bromine	chlorine	

TABLE II

Co-crystal Former							
Asparagine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Asparagine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Asparagine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Aspartic Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Aspartic Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Benzenesulfonic Acid							
Benzoic Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Caffeine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Camphoric acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Capric acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Genistein	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Genistein	nitro	sulfone	analine				
Genistein	ester	ether	carboxylic acid	sulfate	sulfone		alcohol
Cinnamic acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Citric Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Citric Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Clemizole	*bromine		hydroxamic acid	cyano	carboxamide	*sulfonic acid	*phosphoric acid
Cyclamic Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Cydamic Acid							
Cysteine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Cysteine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Cysteine							
Dimethylglycine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Dimethylglycine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
D-ribose	ester	ether	carboxylic acid	sulfate	sulfone		alcohol
D-ribose	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Fumaric Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Galactaric acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Galactaric acid	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		fluorine
Chrysin	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	

TABLE II

Co-crystal Former								
Asparagine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Asparagine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Asparagine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Aspartic Acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Aspartic Acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Benzenesulfonic Acid								
Benzoic Acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Caffeine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Camphoric acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Capric acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Genistein	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Genistein								
Genistein		phosphate	cyanamide					
Cinnamic acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Citric Acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Citric Acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Clemizole	N-oxide	ester	ether	fluorine	acetate	thione	dithiadiazocyclopentadienyl	
Cyclamic Acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Cyclamic Acid								
Cysteine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Cysteine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Cysteine								
Dimethylglycine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Dimethylglycine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
D-ribose		phosphate	cyanamide					
D-ribose	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Fumaric Acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Galactaric acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Galactaric acid	carbamate	imidazole	BF4				N-SO2	thiourea
Chrysin	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea

TABLE II

Co-crystal Former			
Asparagine	iodine		
Asparagine	iodine	epoxide	peroxide
Asparagine	iodine		
Aspartic Acid	iodine		
Aspartic Acid	iodine		
Benzenesulfonic Acid			
Benzoic Acid	iodine		
Caffeine	iodine		
Camphoric acid	iodine		
Capric acid	iodine		
Genistein	iodine		
Genistein			
Genistein			
Cinnamic acid	iodine		
Citric Acid	iodine	epoxide	
Citric Acid	iodine		
Clemizole			
Cyclamic Acid	iodine		
Cyclamic Acid			
Cysteine	iodine		
Cysteine	iodine		
Cysteine			
Dimethylglycine	iodine		
Dimethylglycine	iodine		
D-ribose			
D-ribose	iodine	epoxide	
Fumaric Acid	iodine		
Galactaric acid	iodine		
Galactaric acid	iodine		
Chrysin	iodine		

TABLE II

Co-crystal Former	Co-crystal Former Functional Group	Interacting Group						
Chrysin	Phenol	amine	amide	sulfoxide	n	pyridine	cyano	aldehyde
Chrysin	Ether	aromatic-N	amide	amine	aromatic_s	Sp2 amine	sulfoxide	chlorate
Gentisic acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Gentisic acid	Phenol	amine	amide	sulfoxide	n	pyridine	cyano	aldehyde
Glucamine, N-methyl	alcohol	alcohol	ketone	thiol	amide	amine	analine	phenol
Glucamine, N-methyl	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol
Gluconic Acid	Alcohol	alcohol	ketone	thiol	amide	amine	analine	phenol
Gluconic Acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Glucosamine	alcohol	alcohol	ketone	thiol	amide	amine	analine	phenol
Glucuronic acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Glucuronic acid	alcohol	alcohol	ketone	thiol	amide	amine	analine	phenol
Glucuronic acid	Aldehyde	alcohol	ketone	thiol	amide	amine	analine	phenol
Glutamic Acid	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol
Glutamic Acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Glutamine	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol
Glutamine	Amide	alcohol	ketone	thiol	amide	amine	analine	phenol
Glutamine	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Glutaric Acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Glycine	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol
Glycine	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Glycolic Acid	Alcohol	alcohol	ketone	thiol	amide	amine	analine	phenol
Glycolic Acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Hippuric Acid	Amide	alcohol	ketone	thiol	amide	amine	analine	phenol
Hippuric Acid	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol
Hippuric Acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Histidine	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol
Histidine	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Histidine	Imidazole	imidazole	chlorine	acetamide	carboxylate		thione	nitro
Hydroquinone	Alcohol	alcohol	ketone	thiol	amide	amine	analine	phenol
Hydroquinone	Phenol	amine	amide	sulfoxide	n	pyridine	cyano	aldehyde
Imidazole	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol

TABLE II

Co-crystal Former								
Chrysin		alchohol		ester	ether	n-oxide	chlorine	fluorine
Chrysin	chlorine		cyano	ester	amine	nitro	nitrate	bromine
Gentisic acid	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Gentisic acid		alchohol		ester	ether	n-oxide	chlorine	fluorine
Glucamine, N-methyl	phosphate	sulfate	sulfone	nitrate	pyridine	carboxilic acid	metals	aldehyde
Glucamine, N-methyl	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Gluconic Acid	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals
Gluconic Acid	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Glucosamine	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals
Glucuronic acid	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Glucuronic acid	phosphate	sulfate	sulfone	nitrate	pyridine	carboxilic acid	metals	aldehyde
Glucuronic acid	phosphate	sulfate	sulfone	nitrate	pyridine	aromatic	carboxilic acid	metals
Glutamic Acid	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Glutamic Acid	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Glutamine	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Glutamine	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals
Glutamine	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Glutaric Acid	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Glycine	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Glycine	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Glycolic Acid	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals
Glycolic Acid	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Hippuric Acid	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Hippuric Acid	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Hippuric Acid	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Histidine	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Histidine	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Histidine	cyanamide	ketone	cyano	Carboxylic Acid	alcohol		thiol	amine
Hydroquinone	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals
Hydroquinone		alchohol		ester	ether	n-oxide	chlorine	fluorine
Imidazole	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals

TABLE II

Co-crystal Former								
Chrysin	bromine	iodine	ketone	sulfonic acid	sulfate	phosphate	phosphonic acid	carboxylic acid
Chrysin	aldehyde	ketone	peroxide	epoxide			heterocyclic-S	iodine
Gentisic acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Gentisic acid	bromine	iodine	ketone	sulfonic acid	sulfate	phosphate	phosphonic acid	carboxylic acid
Glucamine, N-methyl	ester	ether	cyano		furan	bromine	chlorine	s-heterocyclic
Glucamine, N-methyl	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Gluconic Acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Gluconic Acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Glucosamine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Glucuronic acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Glucuronic acid	ester	ether	cyano		furan	bromine	chlorine	s-heterocyclic
Glucuronic acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Glutamic Acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Glutamic Acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Glutamine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Glutamine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Glutamine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Glutaric Acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Glycine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Glycine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Glycolic Acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Glycolic Acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Hippuric Acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Hippuric Acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Hippuric Acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Histidine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Histidine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Histidine	phosphinic acid hemihydrate	chlorine	sulfonyl	sulfoxide	amide	fluorine	sulfonate ester	
Hydroquinone	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Hydroquinone	bromine	iodine	ketone	sulfonic acid	sulfate	phosphate	phosphonic acid	carboxylic acid
Imidazole	aldehyde	ester	ether	cyano		furan	bromine	chlorine

TABLE II

Co-crystal Former								
Chrysin	nitro	sulfone	analine					
Chrysin	ester	ether	carboxylic acid	sulfate	sulfone			alcohol
Gentisic acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		
Gentisic acid	nitro	sulfone	analine					
Glucamine, N-methyl	pyridine	cyano	n-heterocyclic	ketone	phosphate ester			fluorine
Glucamine, N-methyl	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		
Gluconic Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		
Gluconic Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		
Glucosamine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		
Glucuronic acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		
Glucuronic acid	pyridine	cyano	n-heterocyclic	ketone	phosphate ester			fluorine
Glucuronic acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		
Glutamic Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		
Glutamic Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		
Glutamine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		
Glutamine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		
Glutamine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		
Glutaric Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		
Glycine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		
Glycine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		
Glycolic Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		
Glycolic Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		
Hippuric Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		
Hippuric Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		
Hippuric Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		
Histidine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		
Histidine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		
Histidine								
Hydroquinone	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		
Hydroquinone	nitro	sulfone	analine					
Imidazole	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		

TABLE II

Co-crystal Former									
Chrysin									
Chrysin		phosphate	cyanamide						
Genistic acid	fluorine	carbamate	imidazole	BF4			N-SO2		thiourea
Genistic acid									
Glucamine, N-methyl	carbamate	limidazole	BF4						
Glucamine, N-methyl	fluorine	carbamate	imidazole	BF4			N-SO2		thiourea
Gluconic Acid	fluorine	carbamate	imidazole	BF4			N-SO2		thiourea
Gluconic Acid	fluorine	carbamate	imidazole	BF4			N-SO2		thiourea
Glucosamine	fluorine	carbamate	imidazole	BF4			N-SO2		thiourea
Glucuronic acid	fluorine	carbamate	imidazole	BF4			N-SO2		thiourea
Glucuronic acid	carbamate	imidazole	BF4						
Glucuronic acid	fluorine	carbamate	imidazole	BF4	alkane	aromatic	N-SO2		thiourea
Glutamic Acid	fluorine	carbamate	imidazole	BF4			N-SO2		thiourea
Glutamic Acid	fluorine	carbamate	imidazole	BF4			N-SO2		thiourea
Glutamine	fluorine	carbamate	imidazole	BF4			N-SO2		thiourea
Glutamine	fluorine	carbamate	imidazole	BF4			N-SO2		thiourea
Glutamine	fluorine	carbamate	imidazole	BF4			N-SO2		thiourea
Glutaric Acid	fluorine	carbamate	imidazole	BF4			N-SO2		thiourea
Glycine	fluorine	carbamate	imidazole	BF4			N-SO2		thiourea
Glycine	fluorine	carbamate	imidazole	BF4			N-SO2		thiourea
Glycolic Acid	fluorine	carbamate	imidazole	BF4			N-SO2		thiourea
Glycolic Acid	fluorine	carbamate	imidazole	BF4			N-SO2		thiourea
Hippuric Acid	fluorine	carbamate	imidazole	BF4			N-SO2		thiourea
Hippuric Acid	fluorine	carbamate	imidazole	BF4			N-SO2		thiourea
Hippuric Acid	fluorine	carbamate	imidazole	BF4			N-SO2		thiourea
Histidine	fluorine	carbamate	imidazole	BF4			N-SO2		thiourea
Histidine	fluorine	carbamate	imidazole	BF4			N-SO2		thiourea
Histidine									
Hydroquinone	fluorine	carbamate	imidazole	BF4			N-SO2		thiourea
Hydroquinone									
imidazole	fluorine	carbamate	imidazole	BF4			N-SO2		thiourea

TABLE II

Co-crystal Former			
Chrysin			
Chrysin			
Gentisic acid	Iodine		
Gentisic acid			
Glucamine, N-methyl			
Glucamine, N-methyl	Iodine		
Gluconic Acid	Iodine	epoxide	
Gluconic Acid	Iodine		
Glucosamine	Iodine	epoxide	
Glucuronic acid	Iodine		
Glucuronic acid			
Glucuronic acid	Iodine	epoxide	
Glutamic Acid	Iodine		
Glutamic Acid	Iodine		
Glutamine	Iodine		
Glutamine	Iodine	epoxide	peroxide
Glutamine	Iodine		
Glutaric Acid	Iodine		
Glycine	Iodine		
Glycine	Iodine		
Glycolic Acid	Iodine	epoxide	
Glycolic Acid	Iodine		
Hippuric Acid	Iodine	epoxide	peroxide
Hippuric Acid	Iodine		
Histidine	Iodine		
Histidine	Iodine		
Histidine	Iodine		
Histidine			
Hydroquinone	Iodine	epoxide	
Hydroquinone			
Imidazole	Iodine		

TABLE II

Co-crystal Former	Co-crystal Former Functional Group	Interacting Group						
Ipriflavone	Ether	aromatic-N	amide	amine	aromatic_s	Sp2 amine	sulfoxide	chlorate
Ipriflavone	Ketone	alcohol		thiol	amide	amine	analine	phenol
Isoleucine	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol
Isoleucine	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
lactobionic acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Lactobionic acid	alcohol	alcohol	ketone	thiol	amide	amine	analine	phenol
Lactobionic acid	Ether	aromatic-N	amide	amine	aromatic_s	Sp2 amine	sulfoxide	chlorate
Lauric acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Leucine	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Leucine	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol
Lysine	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol
Lysine	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Maleic	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Malic Acid	Alcohol	alcohol	ketone	thiol	amide	amine	analine	phenol
Malic Acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Malonic	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Mandelic Acid	Alcohol	alcohol	ketone	thiol	amide	amine	analine	phenol
Mandelic Acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Methionine	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol
Methionine	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Methionine	Thioether	-N	amide	amine	_s	Sp2 amine	sulfoxide	chlorate
Nicotinamide	Pyridine	*alcohol		*	*amide	nitro	*amine	*Carboxylic Acid
Nicotinamide	Amide	alcohol	ketone	thiol	amide	amine	analine	phenol
Nicotinic Acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Nicotinic Acid	Pyridine	*alcohol		*	*amide	nitro	*amine	*Carboxylic Acid
Orotic acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Orotic acid	Lactam	alcohol	ketone	thiol	amide	amine	analine	phenol
Oxalic acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Palmitic acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Pamoic acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Pamoic acid	alcohol	alcohol	ketone	thiol	amide	amine	analine	phenol
Pamoic acid	Phenol	amine	amide	sulfoxide	n	pyridine	cyano	aldehyde

TABLE II

Co-crystal Former									
Ipriflavone	chlorine		cyano	ester	amine	nitro	nitrate		bromine
Ipriflavone	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid		metals
Isoleucine	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid		metals
Isoleucine	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid		metals
lactobionic acid	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid		metals
Lactobionic acid	phosphate	sulfate	sulfone	nitrate	pyridine	carboxilic acid	metals		aldehyde
Lactobionic acid	chlorine		cyano	ester	amine	nitro	nitrate		bromine
Lauric acid	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid		
Leucine	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid		metals
Leucine	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid		metals
Lysine	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid		metals
Lysine	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid		metals
Maleic	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid		metals
Malic Acid	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid		metals
Malic Acid	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid		metals
Malonic	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid		metals
Mandelic Acid	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid		metals
Mandelic Acid	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid		metals
Methionine	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid		metals
Methionine	chlorine		cyano	ester	amine	nitro	nitrate		bromine
Nicotinamide	*sulfonamide	*ketone	ether	triazole		ammonium	oxime		*chlorine
Nicotinamide	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid		metals
Nicotinic Acid	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid		metals
Nicotinic Acid	*sulfonamide	*ketone	ether	triazole		ammonium	oxime		*chlorine
Orotic acid	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid		
Orotic acid	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid		metals
Oxalic acid	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid		
Palmitic acid	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid		
Pamoic acid	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid		
Pamoic acid	phosphate	sulfate	sulfone	nitrate	pyridine	carboxilic acid	metals		aldehyde
Pamoic acid		alchohol		ester	ether	n-oxide	chlorine		fluorine

TABLE II

Co-crystal Former								
Iprriflavone	aldehyde	ketone	peroxide	epoxide			heterocyclic-S	iodine
iprriflavone	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Isoleucine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Isoleucine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
lactobionic acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Lactobionic acid	ester	ether	cyano		furan	bromine	chlorine	s-heterocyclic
Lactobionic acid	aldehyde	ketone	peroxide	epoxide			heterocyclic-S	iodine
Lauric acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Leucine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Leucine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Lysine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Lysine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Maleic	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Malic Acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Malic Acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Malonic	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Mandelic Acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Mandelic Acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Methionine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Methionine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Methionine	aldehyde	ketone	peroxide	epoxide	Ag	Se	heterocyclic-S	iodine
Nicotinamide		thiol	n-heterocyclic ring	thionedisulfide	pyrrolidindione	iodine	hydrazone	thiocyanate
Nicotinamide	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Nicotinic Acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Nicotinic Acid		thiol	n-heterocyclic ring	thionedisulfide	pyrrolidindione	iodine	hydrazone	thiocyanate
Orotic acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Orotic acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Oxalic acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Palmitic acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Pamoic acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Pamoic acid	ester	ether	cyano		furan	bromine	chlorine	chlorine
Pamoic acid	bromine	iodine	ketone	sulfonic acid	sulfate	phosphate	phosphonic acid	carboxylic acid

TABLE II

Co-crystal Former							
ipriflavone	ester	ether	carboxylic acid	sulfate	sulfone		alcohol
ipriflavone	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
isoleucine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
isoleucine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
lactobionic acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Lactobionic acid	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		fluorine
Lactobionic acid	ester	ether	carboxylic acid	sulfate	sulfone		alcohol
Lauric acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Leucine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Leucine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Lysine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Lysine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Maleic	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Malic Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Malic Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Malonic	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Mandelic Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Mandelic Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Methionine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Methionine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Methionine	ester	ether	carboxylic acid	sulfate	sulfone		alcohol
Nicotinamide	*bromine		hydroxamic acid	cyano	carboxamide	*sulfonic acid	*phosphoric acid
Nicotinamide	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Nicotinic Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Nicotinic Acid	*bromine		hydroxamic acid	cyano	carboxamide	*sulfonic acid	*phosphoric acid
Orotic acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Orotic acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Oxalic acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Palmitic acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Pamoic acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Pamoic acid	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		fluorine
Pamoic acid	nitro	sulfone	analine				

TABLE II

Co-crystal Former									
Iprritiavone		phosphate	cyanamide						
Iprritiavone	fluorine	carbamate	imidazole	BF4			N-SO2		thiourea
isoleucine	fluorine	carbamate	imidazole	BF4			N-SO2		thiourea
Isoleucine	fluorine	carbamate	imidazole	BF4			N-SO2		thiourea
lactobionic acid	fluorine	carbamate	imidazole	BF4			N-SO2		thiourea
Lactobionic acid	carbamate	imidazole	BF4						
Lactobionic acid		phosphate	cyanamide						
Lauric acid	fluorine	carbamate	imidazole	BF4			N-SO2		thiourea
Leucine	fluorine	carbamate	imidazole	BF4			N-SO2		thiourea
Leucine	fluorine	carbamate	imidazole	BF4			N-SO2		thiourea
Lysine	fluorine	carbamate	imidazole	BF4			N-SO2		thiourea
Lysine	fluorine	carbamate	imidazole	BF4			N-SO2		thiourea
Maleic	fluorine	carbamate	imidazole	BF4			N-SO2		thiourea
Malic Acid	fluorine	carbamate	imidazole	BF4			N-SO2		thiourea
Malic Acid	fluorine	carbamate	imidazole	BF4			N-SO2		thiourea
Malonic	fluorine	carbamate	imidazole	BF4			N-SO2		thiourea
Mandelic Acid	fluorine	carbamate	imidazole	BF4			N-SO2		thiourea
Mandelic Acid	fluorine	carbamate	imidazole	BF4			N-SO2		thiourea
Methionine	fluorine	carbamate	imidazole	BF4			N-SO2		thiourea
Methionine	fluorine	carbamate	imidazole	BF4			N-SO2		thiourea
Methionine		phosphate							
Nicotinamide	N-oxide	ester	ether	fluorine	acetate	thione	dithiadiazocyclopentadienyl		
Nicotinamide	fluorine	carbamate	imidazole	BF4			N-SO2		thiourea
Nicotinic Acid	fluorine	carbamate	imidazole	BF4			N-SO2		thiourea
Nicotinic Acid	N-oxide	ester	ether	fluorine	acetate	thione	dithiadiazocyclopentadienyl		
Orotic acid	fluorine	carbamate	imidazole	BF4			N-SO2		thiourea
Orotic acid	fluorine	carbamate	imidazole	BF4			N-SO2		thiourea
Oxalic acid	fluorine	carbamate	imidazole	BF4			N-SO2		thiourea
Palmitic acid	fluorine	carbamate	imidazole	BF4			N-SO2		thiourea
Pamoic acid	fluorine	carbamate	imidazole	BF4			N-SO2		thiourea
Pamoic acid	carbamate	imidazole	BF4						
Pamoic acid									

TABLE II

Co-crystal Former				
Ipriflavone				
Ipriflavone	iodine			
Isoleucine	iodine			
Isoleucine	iodine			
lactobionic acid	iodine			
Lactobionic acid	iodine			
Lactobionic acid				
Lauric acid	iodine			
Leucine	iodine			
Leucine	iodine			
Lysine	iodine			
Lysine	iodine			
Maleic	iodine			
Malic Acid	iodine	epoxide		
Malic Acid	iodine			
Malonic	iodine			
Mandelic Acid	iodine	epoxide		
Mandelic Acid	iodine			
Methionine	iodine			
Methionine	iodine			
Methionine				
Nicotinamide				
Nicotinamide	iodine	epoxide	peroxide	
Nicotinic Acid	iodine			
Nicotinic Acid				
Orotic acid	iodine			
Orotic acid	iodine	epoxide	peroxide	
Oxalic acid	iodine			
Palimitic acid	iodine			
Pamoic acid	iodine			
Pamoic acid				
Pamoic acid				

TABLE II

Co-crystal Former	Co-crystal Former Functional Group	Interacting Group						
Phenylalanine	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol
Phenylalanine	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Piperazine	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol
Procaine	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol
Procaine	Ketone	alcohol		thiol	amide	amine	analine	phenol
Proline	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Proline	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol
p-Toluenesulfonic acid	Sulfonic Acid	pyridine	ketone	aldehyde	ether	ester	amide	Carboxylic Acid
Pyridoxamine	Alcohol	alcohol	ketone	thiol	amide	amine	analine	phenol
Pyridoxamine	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol
Pyridoxamine	Pyridine	*alcohol		*	*amide	nitro	*amine	*Carboxylic Acid
Pyridoxine (4-Pyridoxic Acid)	Pyridine	*alcohol	pyridinium	*	*amide	nitro	*amine	*Carboxylic Acid
Pyridoxine (4-Pyridoxic Acid)	Alcohol	alcohol	ketone	thiol	amide	amine	analine	phenol
Pyroglutamic acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Pyroglutamic acid	Lactam	alcohol	ketone	thiol	amide	amine	analine	phenol
Quercetin	Ketone	alcohol		thiol	amide	amine	analine	phenol
Quercetin	Phenol	amine	amide	sulfoxide	n	pyridine	cyano	aldehyde
Quercetin	Ether	aromatic-N	amide	amine	aromatic_s	Sp2 amine	sulfoxide	chlorate
Resveratrol	Ketone	alcohol		thiol	amide	amine	analine	phenol
Resveratrol	Phenol	amine	amide	sulfoxide	n	pyridine	cyano	aldehyde
Saccharin	Amide	alcohol	ketone	thiol	amide	amine	analine	phenol
Saccharin	Ketone	alcohol		thiol	amide	amine	analine	phenol
Saccharin	Sulfoxide	pyridine	ketone	aldehyde	ether	ester	amide	Carboxylic Acid
Saccharin	Amine	alcohol	ketone	thiol	amide		analine	phenol
Salicylic Acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Salicylic Acid	Alcohol	alcohol	ketone	thiol	amide	amine	analine	phenol
Salicylic Acid, 4-amino	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Salicylic Acid, 4-amino	alcohol	alcohol	ketone	thiol	amide	amine	analine	phenol
Salicylic Acid, 4-amino	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol

TABLE II

Co-crystal Former								
Phenylalanine	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Phenylalanine	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Piperazine	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Procaine	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Procaine	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals
Proline	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Proline	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
p-Toluenesulfonic acid	amine	metals	thioether		sulfate	alcohol		
Pyridoxamine	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals
Pyridoxamine	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Pyridoxamine	*sulfonamide	*ketone	ether	triazole		ammonium	oxime	*chlorine
Pyridoxine (4-Pyridoxic Acid)	*sulfonamide	*ketone	ether	triazole		ammonium	oxime	*chlorine
Pyridoxine (4-Pyridoxic Acid)	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals
Pyroglutamic acid	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Pyroglutamic acid	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals
Quercetin	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals
Quercetin		alchohol		ester	ether	n-oxide	chlorine	fluorine
Quercetin	chlorine		cyano	ester	amine	nitro	nitrate	bromine
Resveratrol	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals
Resveratrol		alchohol		ester	ether	n-oxide	chlorine	fluorine
Saccharin	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals
Saccharin	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals
Saccharin	amine	metals	thioether		sulfate	alcohol		
Saccharin	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals
Salicylic Acid	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Salicylic Acid	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals
Salicylic Acid, 4-amino	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Salicylic Acid, 4-amino	phosphate	sulfate	sulfone	nitrate	pyridine	carboxilic acid	metals	aldehyde
Salicylic Acid, 4-amino	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals

TABLE II

Co-crystal Former									
Phenylalanine	aldehyde	ester	ether	cyano		furan	bromine		chlorine
Phenylalanine	aldehyde	ester	ether	cyano		furan	bromine		chlorine
Piperazine	aldehyde	ester	ether	cyano		furan	bromine		chlorine
Procaine	aldehyde	ester	ether	cyano		furan	bromine		chlorine
Procaine	aldehyde	ester	ether	cyano		furan	bromine		chlorine
Proline	aldehyde	ester	ether	cyano		furan	bromine		chlorine
Proline	aldehyde	ester	ether	cyano		furan	bromine		chlorine
p-Toluenesulfonic acid									
Pyridoxamine	aldehyde	ester	ether	cyano		furan	bromine		chlorine
Pyridoxamine	aldehyde	ester	ether	cyano		furan	bromine		chlorine
Pyridoxamine		thiol	n-heterocyclic ring	thionedisulfide		iodine	hydrazone		thiopyanate
Pyridoxine (4-Pyridoxic Acid)		thiol	n-heterocyclic ring	thionedisulfide	pyrrolidindione	iodine	hydrazone		thiopyanate
Pyridoxine (4-Pyridoxic Acid)	aldehyde	ester	ether	cyano		furan	bromine		chlorine
Pyroglutamic acid	aldehyde	ester	ether	cyano		furan	bromine		chlorine
Pyroglutamic acid	aldehyde	ester	ether	cyano		furan	bromine		chlorine
Quercetin	aldehyde	ester	ether	cyano		furan	bromine		chlorine
Quercetin	bromine	iodine	ketone	sulfonic acid	sulfate	phosphate	phosphonic acid		carboxylic acid
Quercetin	aldehyde	ketone	peroxide	epoxide			heterocyclic-S		iodine
Resveratrol	aldehyde	ester	ether	cyano		furan	bromine		chlorine
Resveratrol	bromine	iodine	ketone	sulfonic acid	sulfate	phosphate	phosphonic acid		carboxylic acid
Saccharin	aldehyde	ester	ether	cyano		furan	bromine		chlorine
Saccharin	aldehyde	ester	ether	cyano		furan	bromine		chlorine
Saccharin	aldehyde	ester	ether	cyano		furan	bromine		chlorine
Salicylic Acid	aldehyde	ester	ether	cyano		furan	bromine		chlorine
Salicylic Acid	aldehyde	ester	ether	cyano		furan	bromine		chlorine
Salicylic Acid, 4-amino	aldehyde	ester	ether	cyano		furan	bromine		chlorine
Salicylic Acid, 4-amino	ester	ether	cyano		furan	bromine	chlorine		s-heterocyclic
Salicylic Acid, 4-amino	aldehyde	ester	ether	cyano		furan	bromine		chlorine

TABLE II

Co-crystal Former							
Phenylalanine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Phenylalanine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Piperazine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Procaine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Procaine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Proline	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Proline	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
p-Toluenesulfonic acid							
Pyridoxamine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Pyridoxamine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Pyridoxamine	*bromine		hydroxamic acid	cyano	carboxamide	*sulfonic acid	*phosphoric acid
Pyridoxine (4-Pyridoxic Acid)	*bromine		hydroxamic acid	cyano	carboxamide	*sulfonic acid	*phosphoric acid
Pyridoxine (4-Pyridoxic Acid)	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Pyroglutamic acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Pyroglutamic acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Quercetin	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Quercetin	nitro	sulfone	analine				
Quercetin	ester	ether	carboxylic acid	sulfate	sulfone		alcohol
Resveratrol	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Resveratrol	nitro	sulfone	analine				
Saccharin	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Saccharin	s-heterocyclic	pyridine	*cyano	n-heterocyclic	ketone	phosphate ester	
Saccharin	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Salicylic Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Salicylic Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Salicylic Acid, 4-amino	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Salicylic Acid, 4-amino	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		fluorine
Salicylic Acid, 4-amino	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	

TABLE II

Co-crystal Former								
Phenylalanine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Phenylalanine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Piperazine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Procaine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Procaine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Proline	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Proline	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
p-Toluenesulfonic acid								
Pyridoxamine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Pyridoxamine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Pyridoxamine	N-oxide	ester	ether	fluorine	acetate	thione	dithiadiazocyclopentadienyl	
Pyridoxine (4-Pyridoxic Acid)	N-oxide	ester	ether	fluorine	acetate	thione	dithiadiazocyclopentadienyl	
Pyridoxine (4-Pyridoxic Acid)	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Pyroglutamic acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Pyroglutamic acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Quercetin	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Quercetin		phosphate	cyanamide					
Resveratrol	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Resveratrol								
Saccharin	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Saccharin	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Saccharin	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Salicylic Acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Salicylic Acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Salicylic Acid, 4-amino	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Salicylic Acid, 4-amino	carbamate	imidazole	BF4				N-SO2	thiourea
Salicylic Acid, 4-amino	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea

TABLE II

Co-crystal Former			
Phenylalanine	iodine		
Phenylalanine	iodine		
Piperazine	iodine		
Procaine	iodine		
Procaine	iodine		
Proline	iodine		
Proline	iodine		
p-Toluenesulfonic acid			
Pyridoxamine	iodine	epoxide	
Pyridoxamine	iodine		
Pyridoxamine			
Pyridoxine (4-Pyridoxic Acid)			
Pyridoxine (4-Pyridoxic Acid)	iodine	epoxide	
Pyroglutamic acid	iodine		
Pyroglutamic acid	iodine	epoxide	peroxide
Quercetin	iodine		
Quercetin			
Resveratrol	iodine		
Resveratrol			
Saccharin	iodine	epoxide	peroxide
Saccharin	iodine		
Saccharin	iodine		
Salicylic Acid	iodine		
Salicylic Acid	iodine	epoxide	
Salicylic Acid, 4-amino	iodine		
Salicylic Acid, 4-amino			
Salicylic Acid, 4-amino	iodine		

TABLE II

Co-crystal Former	Co-crystal Former Functional Group	Interacting Group						
Sebacic acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Serine	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Serine	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Serine	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol
Serine	Alcohol	alcohol	ketone	thiol	amide	amine	analine	phenol
Stearic acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Succinic Acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Tartaric Acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Threonine	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol
Threonine	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Threonine	alcohol	alcohol	ketone	thiol	amide	amine	analine	phenol
Tris	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol
Tris	Alcohol	alcohol	ketone	thiol	amide	amine	analine	phenol
Tryptophan	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol
Tryptophan	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Tryptophan	Indole	*alcohol	pyridinium	*	*amide	nitro	*amine	*carboxilic acid
Tyrosine	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol
Tyrosine	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Tyrosine	Alcohol	alcohol	ketone	thiol	amide	amine	analine	phenol
Urea	Ketone	alcohol		thiol	amide	amine	analine	phenol
Urea	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol
Urea	Amide	alcohol	ketone	thiol	amide	amine	analine	phenol
Valine	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol
Valine	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine	phenol
Vitamin K5	Amine	alcohol	ketone	thiol	amide	amine	analine	phenol
Vitamin K5	Alcohol	alcohol	ketone	thiol	amide	amine	analine	phenol
Xylitol	Alcohol	alcohol	ketone	thiol	amide	amine	analine	phenol

TABLE II

Co-crystal Former								
Sebacic acid	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Serine	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals
Serine	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Serine	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals
Stearic acid	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Succinic Acid	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals
Tartaric Acid	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals
Threonine	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Threonine	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Threonine	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals
Tris	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Tris	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals
Tryptophan	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Tryptophan	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Tryptophan	*sulfonamide	*ketone	ether	triazole		ammonium	oxime	*chlorine
Tyrosine	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Tyrosine	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Tyrosine	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals
Urea	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals
Urea	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Urea	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals
Valine	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Valine	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Vitamin K5	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid	metals
Vitamin K5	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals
Xylitol	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid	metals

TABLE II

Co-crystal Former								
Sebacic acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Serine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Serine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Serine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Stearic acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Succinic Acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Tartaric Acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Threonine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Threonine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Threonine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Tris	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Tris	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Tryptophan	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Tryptophan	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Tryptophan		thiol	n-heterocyclic ring	thionedisulfide	pyrrolidindione	iodine	hydrazone	thiocyanate
Tyrosine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Tyrosine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Tyrosine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Urea	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Urea	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Urea	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Valine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Valine	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Vitamin K5	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Vitamin K5	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Xylitol	aldehyde	ester	ether	cyano		furan	bromine	chlorine

TABLE II

Co-crystal Former							
Sebacic acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Serine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Serine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Serine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Stearic acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Succinic Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Tartaric Acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Threonine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Threonine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Threonine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Tris	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Tris	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Tryptophan	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Tryptophan	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Tryptophan	*bromine		hydroxamic acid	cyano	carboxamide	*sulfonic acid	*phosphoric acid
Tyrosine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Tyrosine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Tyrosine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Urea	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Urea	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Urea	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Valine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Valine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Vitamin K5	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Vitamin K5	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	
Xylitol	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester	

TABLE II

Co-crystal Former								
Sebacic acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Serine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Serine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Serine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Stearic acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Succinic Acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Tartaric Acid	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Threonine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Threonine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Threonine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Tris	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Tris	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Tryptophan	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Tryptophan	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
								thiourea
Tryptophan	N-oxide	ester	ether	fluorine	acetate	thione	dithiadiazocyclopentadienyl	
Tyrosine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Tyrosine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Tyrosine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Urea	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Urea	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Urea	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Valine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Valine	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Vitamin K5	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Vitamin K5	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
Xylitol	fluorine	carbamate	imidazole	BF4			N-SO2	thiourea
								thiourea

TABLE II

Co-crystal Former			
Sebacic acid	iodine		
Serine	iodine		
Serine	iodine		
Serine	iodine	epoxide	
Stearic acid	iodine		
Succinic Acid	iodine		
Tartaric Acid	iodine		
Threonine	iodine		
Threonine	iodine		
Threonine	iodine	epoxide	
Tris	iodine		
Tris	iodine	epoxide	
Tryptophan	iodine		
Tryptophan	iodine		
Tryptophan			
Tyrosine	iodine		
Tyrosine	iodine		
Tyrosine	iodine	epoxide	
Urea	iodine		
Urea	iodine		
Urea	iodine	epoxide	peroxide
Valine	iodine		
Valine	iodine		
Vitamin K5	iodine		
Vitamin K5	iodine	epoxide	
Xylitol	iodine	epoxide	

TABLE III

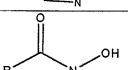
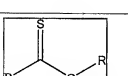
Functional Group	Functional Group Structure	Interacting Group					
pyridine		*alcohol	pyridinium	*amide	nitro	*amine	*carboxilic acid
imidazole		imidazole	chlorine	acetamide	carboxylate	thione	nitro
Hydroxamic acid		hydroxamic acid	alcohol	phosphinic ester	alkane	pyridine	amide
peroxide		ester	peroxide	amide	ether	alkane	N-heterocycle
epoxide		alkane	bromine	alcohol	ester	epoxide	amide
thioester		aromatic	thioester	alkane	sulfamide	hydroxy	bromine

TABLE III

Functional Group													
pyridine	*sulfonamide	*ketone	ether	triazole	alkane	ammonium	oxime	*chlorine	alkyne				
imidazole	cyanamide	ketone	cyano	carboxilic acid	alcohol	alkane	thiol	amine	phosphinic acid hemihydrate				
Hydroxamic acid	sulfonamide	carboxylate	phosphine	amine	aromatic								
peroxide	aromatic	alcohol	pyrimidinedione	aniline	thiazole	peroxy acid	ketone	carboxilic acid	azide				
epoxide	alkene	hydrazone	aromatic	thioether	ketone	aldehyde	chlorine	carboxilic acid	alkyne				
thioester	iodine	amine	cyano	thioketone	amide		chlorine	nitro					

TABLE III

Functional Group											
pyridine	thiol	n-heterocyclic ring	thionedisulfide	pyrrolidindione	iodine	hydrazone	thiocyanate	*bromine	aromatic		
imidazole	chlorine	sulfonyl	sulfoxide	amide	fluorine	sulfonate ester					
Hydroxamic acid											
peroxide	phosphine oxide	sulfonamide	analine								
epoxide		ammonium	fluorine	nitro	amine	cyano					
thioester											

TABLE III

Functional Group	hydroxamic acid	cyano	carboxamide	*sulfonic acid	*phosphoric acid	N-oxide	ester	ether	fluorine	acetate	thione
pyridine											
imidazole											
Hydroxamic acid											
peroxide											
epoxide											
thioester											

TABLE III

Functional Group						
pyridine	dithiadiazocyclopentadienyl					
imidazole						
Hydroxamic acid						
peroxide						
epoxide						
thioester						

TABLE III

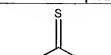
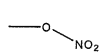
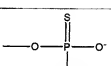
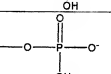
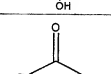
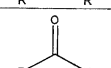
Functional Group	Functional Group Structure	Interacting Group					
thioketone		alkane	thioketone	ketone	SULFAMIDE	AMINE	thiol
nitrate ester		aromatic	amide	alkane	chlorine	nitrate ester	bromine
Thiophosphate ester-O		amine	imidazole	cyclic amide			
Phosphate ester		aromatic	alcohol	phosphate ester	aromatic N-ring	pyridine	analine
Ketone		alcohol	ketone	thiol	amide	amine	analine
Aldehyde		alcohol	ketone	thiol	amide	amine	analine
Thiol		carboxylic acid	sodium	aldehyde	ketone	aromatic-N	cadmium

TABLE III

Functional Group												
thioketone	sulfoxide	oxo	chlorine	bromine	AROMATIC	alkene	sulfone	iodine	AZOXY			
nitrate ester	alcohol	ether	acetate									
Thiophosphate ester-O												
Phosphate ester	amine		sodium	potassium	lithium	carboxylic acid	amide	alkane				
Ketone	phenol	phosphate	sulfate	sulfone	nitrate	pyridine	aromatic	carboxilic acid	metals			
Aldehyde	phenol	phosphate	sulfate	sulfone	nitrate	pyridine	aromatic	carboxilic acid	metals			
Thiol	alkane	arsenic	chlorine	alcohol	potassium	Ru	aromatic	Rb	Sb			

TABLE III

Functional Group											
thioketone	potassium	epoxide	n-oxide	cyano	iron	cobalt	amine	sulfate			
nitrate ester											
Thiophosphate ester-O											
Phosphate ester											
Ketone	aldehyde	ester	ether	cyano		furan	bromine	chlorine	s-heterocyclic		
Aldehyde	aldehyde	ester	ether	cyano		furan	bromine	chlorine	s-heterocyclic		
Thiol											

TABLE III

Functional Group																		
thioketone																		
nitrate ester																		
Thiophosphate ester-O																		
Phosphate ester																		
Ketone	pyridine	cyano	n-heterocyclic	ketone	phosphate ester			fluorine	carbamate	imidazole	BF4	alkane						
Aldehyde	pyridine	cyano	n-heterocyclic	ketone	phosphate ester			fluorine	carbamate	imidazole	BF4	alkane						
Thiol																		

TABLE III

Functional Group							
thioketone							
nitrate ester							
Thiophosphate ester-O							
Phosphate ester							
Ketone	aromatic	N-SO2	thiourea	iodine			
Aldehyde	aromatic	N-SO2	thiourea	iodine	epoxide		
Thiol							

TABLE III

Functional Group	Functional Group Structure	Interacting Group						
Alcohol		alcohol	ketone	thiol	amide	amine	aniline	
Thioether		aromatic-N	amide	amine	aromatic_s	Sp2 amine	sulfoxide	
Ether		aromatic-N	amide	amine	aromatic_s	Sp2 amine	sulfoxide	
Cyanamide		cyano	amine	potassium	aromatic-N	bromine	sodium	
Thiocyanate		aromatic-S	ester	ether				
sP2 amine		thioether	ether	metals	MoOCl4	BF4	bromine	
Amine primary		alcohol	ketone	thiol	amide	amine	aniline	

TABLE III

Functional Group											
Alcohol	phenol	phosphate	sulfate	sulfone	nitrate	pyridine	aromatic	carboxilic acid	metals		
Thioether	chlorate	chlorine	alkyne	cyano	ester	amine	nitro	nitrate	bromine		
Ether	chlorate	chlorine	alkyne	cyano	ester	amine	nitro	nitrate	bromine		
Cyanamide	imidazole	ether	n-heterocyclic	alcohol	cesium	Ag					
Thiocyanate											
sP2 amine	chlorine		Sp2 amine	sulfate	Osmium						
Amine primary	phenol	phosphate	sulfate	sulfone	nitrate	pyridine	aromatic	carboxilic acid	metals		

TABLE III

Functional Group											
Alcohol	aldehyde	ester	ether	cyano		furan	bromine	chlorine	s-heterocyclic		
Thioether	aldehyde	ketone	peroxide	epoxide	Ag	Se	heterocyclic-S	iodine	ester		
Ether	aldehyde	ketone	peroxide	epoxide	Ag	Se	heterocyclic-S	iodine	ester		
Cyanamide											
Thiocyanate											
isP2 amine											
Amine primary	aldehyde	ester	ether	cyano		furan	bromine	chlorine	s-heterocyclic		

TABLE III

Functional Group														
Alcohol	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		fluorine	carbamate	imidazole	BF4	alkane			
Thioether	ether	carboxylic acid	sulfate	sulfone	alkane	alcohol		phosphate						
Ether	ether	carboxylic acid	sulfate	sulfone	alkane	alcohol		phosphate	cyanamide					
Cyanamide														
Thiocyanate														
sP2 amine														
Amine primary	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		fluorine	carbamate	imidazole	BF4	alkane			

TABLE III

Functional Group							
Alcohol	aromatic	N-SO2	thiourea	iodine	epoxide		
Thioether							
Ether							
Cyanamide							
Thiocyanate							
sP2 amine							
Amine primary	aromatic	N-SO2	thiourea	iodine			

TABLE III

Functional Group	Functional Group Structure	Interacting Group					
Amine secondary		alcohol	ketone	thiol	amide	amine	analine
Amine tertiary		alcohol	ketone	thiol	amide	amine	analine
Amide		alcohol	ketone	thiol	amide	amine	analine
Sulfonic acid		pyridine	ketone	aldehyde	ether	ester	amide
Phosphinic acid		alkane	potassium	lithium	n-heterocyclic	oxime	amide
Phosphonic acid		alkane	potassium	lithium	n-heterocyclic	oxime	amide
Carboxylic acid		alcohol	ketone	thiol	amide	amine	analine

TABLE III

Functional Group											
Amine secondary	phenol	phosphate	sulfate	sulfone	nitrate	pyridine	aromatic	carboxilic acid	metals		
Amine tertiary	phenol	phosphate	sulfate	sulfone	nitrate	pyridine	aromatic	carboxilic acid	metals		
Amide	phenol	phosphate	sulfate	sulfone	nitrate	pyridine	aromatic	carboxilic acid	metals		
Sulfonic acid	carboxilic acid	amine	metals	thioether		sulfate	alcohol				
Phosphinic acid	phenol	aromatic	amine	alcohol		metals					
Phosphonic acid	phenol	aromatic	amine	alcohol		metals	carboxylic acid	Sp2 amine	analine		
Carboxylic acid	phenol	phosphate	sulfate	sulfone	nitrate	pyridine	aromatic	carboxilic acid	metals		

TABLE III

Functional Group											
Amine secondary	aldehyde	ester	ether	cyano		furan	bromine	chlorine	s-heterocyclic		
Amine tertiary	aldehyde	ester	ether	cyano		furan	bromine	chlorine	s-heterocyclic		
Amide	aldehyde	ester	ether	cyano		furan	bromine	chlorine	s-heterocyclic		
Sulfonic acid											
Phosphinic acid											
Phosphonic acid	ether	phosphonic acid	aromatic-N	ketone	aldehyde	imidazole					
Carboxylic acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine	s-heterocyclic		

TABLE III

Functional Group												
Amine secondary	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		fluorine	carbamate	imidazole	BF4		alkane
Amine tertiary	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		fluorine	carbamate	imidazole	BF4		alkane
Amide	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		fluorine	carbamate	imidazole	BF4		alkane
Sulfonic acid												
Phosphinic acid												
Phosphonic acid												
Carboxylic acid	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		fluorine	carbamate	imidazole	BF4		alkane

TABLE III

Functional Group							
Amine secondary	aromatic	N-SO2	thiourea	iodine			
Amine tertiary	aromatic	N-SO2	thiourea	iodine			
Amide	aromatic	N-SO2	thiourea	iodine	epoxide	peroxide	
Sulfonic acid							
Phosphinic acid							
Phosphonic acid							
Carboxylic acid	aromatic	N-SO2	thiourea	iodine			

TABLE III

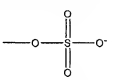
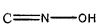
Functional Group	Functional Group Structure	Interacting Group					
Sulfate ester		pyridine	ketone	aldehyde	ether	ester	amide
Oxime		alcohol	alkane	amine	amide	ether	ester
Nitrile		metal	ketone	phenol	alcohol		cyano
Diazo		Oxime					
Nitro		pyridine	ketone	aldehyde	ether	ester	amide
S-heterocyclic ring		alcohol	thioketone	thioether	s-heterocyclic	ketone	aromatic
Thiophene		chlorine	fluorine	amide	ketone	NO	SO

TABLE III

Functional Group												
Sulfate ester	carboxilic acid	amine	metals	thioether	sulfate	alcohol						
Oxime	pyridine	n-aromatic	chlorate	chlorine	Sp2-N	diazo	thioketone	cyano	n-heterocyclic	aromatic		
Nitrile	amine	analine	bromine	amide	alkane	carboxylic acid	chlorine	n-heterocyclic	aromatic			
Diazo												
Nitro	carboxilic acid	amine	metals	thioether	sulfate	alcohol						
S-heterocyclic ring	alkane	amine	chlorine	BF4	sulfate	ester	NO	ether	amide			
Thiophene	CO											

TABLE III

Functional Group													
Sulfate ester													
Oxime	ketone	aldehyde	carboxylic acid	bromine	aromatic	pyridine	BF4						
Nitrile	potassium	aldehyde	thioether	pyridine	n-aromatic	bromine	ether	s-aromatic	thiophene				
Diazo													
Nitro													
S-heterocyclic ring	iodine	carboxylic acid	sodium	cyano	chloride	furan							
Thiophene													

TABLE III

Functional Group													
Sulfate ester													
Oxime													
Nitrile													
Diazo													
Nitro													
S-heterocyclic ring													
Thiophene													